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Incidence, characteristics and morbidity in a Danish nationwide study

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PSYCHOGENIC NONEPILEPTIC SEIZURES IN CHILDREN AND ADOLESCENTS

INCIDENCE, CHARACTERISTICS AND MORBIDITY
IN A DANISH NATIONWIDE STUDY

BY
ANNE SOFIE HANSEN

DISSERTATION SUBMITTED 2020



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AALBORG UNIVERSITY
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Dissertation submitted 2020

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PhD supervisor: Professor René Ernst Nielsen, PhD
Aalborg University, Denmark

Assistant PhD supervisors: Professor Charlotte Ulrikka Rask, PhD
Aarhus University, Denmark
Associate professor Jakob Christensen, Dr.Med.Sci.
Aarhus University, Denmark

PhD committee: Clinical Professor Janus Laust Thomsen (chairman)
Aalborg University
Professor Isobel Heyman
Great Ormond Street Hospital for Children
Professor Morten Lossius
Oslo University Hospital

PhD Series: Faculty of Medicine, Aalborg University

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CURRICULUM VITAE

Anne Sofie Hansen

Date of birth: 10 June, 1980

Contact details: Unit for Psychiatric Research, Psychiatry,
Aalborg University Hospital, Denmark

E-mail address: ansoha@rn.dk



Education:

Feb 2001 - Jan 2008: Medical School, MD. Faculty of Health, Aarhus University, Denmark.

Employment:

April 2008 – Sept 2008: Department of Urology, Aalborg Hospital, Internship.

Oct 2008 – March 2009: Department of Haematology, Aalborg Hospital, Internship.

April 2009 – Sept 2009: General Medicine, Aalborg, Internship.

Oct 2009 – March 2010: General Medicine, Aalborg, Junior Doctor first-year residency.

April 2010 – Oct 2010: Department of Oncology, Aalborg Hospital, Junior Doctor first-year residency.

Nov 2010 – Feb 2011: General Medicine, Aalborg, General Medicine Specialist Training.

May 2012 – Aug 2012: Department of Gynaecology, Aalborg Hospital, General Medicine Specialist Training.

Sept 2012 – Nov 2013: Department of Child and Adolescent Psychiatry, Aalborg, Junior Doctor first-year residency.

Dec 2013 – Feb 2014: Department of Child and Adolescent Psychiatry, Aalborg, Junior Doctor.

March 2014 – April 2016: Department of Child and Adolescent Psychiatry, Aalborg, Specialist Training.

May 2016 - current date: Unit for Psychiatric Research, Psychiatry, Aalborg University Hospital, Junior Doctor, research assistant, and PhD student.

Communication of scientific knowledge:

Mar 2017: Presentation of the PhD study at workshop organized by Dr. Jon Stone, Edinburgh University, held at the Department of Psychiatry, Odense University hospital.

June 2017: Poster presentation at the EAPM (European Association of Psychosomatic medicine) conference in Barcelona, Spain.

- Sept 2017: Poster and oral presentation at the FND (Functional Neurological Disorders) conference in Edinburgh, Scotland.
- April 2018: Speaker at Trygfonden conference, Copenhagen, Denmark: “Functional disorders in children” – presenting the PhD project as well as a project on the development of patient information material.
- July 2018: Poster presentation at the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP) conference in Prague, Czech Republic.
- March 2019: Speaker at the annual meeting of the Danish Association of Child and Adolescent Psychiatrists (BUP-DK): “Workshop on functional disorders in children”, Nyborg, Denmark.
- June 2019: Speaker at the EAPM (European Association of Psychosomatic Medicine) conference, Rotterdam, the Netherlands, presenting results from the PhD project.
- June 2019: Poster presentation at the ESCAP (European Society of Child and Adolescent Psychiatry) conference in Vienna, Austria.
- Sept 2019: Speaker at a conference on children with functional disorders at the Department of Paediatrics, Kolding Hospital, Denmark, presenting results from the PhD project.
- Oct 2019: Speaker at the annual meeting of the Danish College of General Practitioners (DSAM) in Kolding, Denmark, presenting a talk for the medical student association on children and adolescents with functional seizures including results from the PhD project.
- Oct 2019: Speaker at the AACAP (American Academy of Child and Adolescent Psychiatry) conference in Chicago, USA, presenting results from the first study of the PhD project.

Publication list (not part of the PhD thesis):

Hansen AS, Rask CU, Christensen J, Nielsen RE. Baseline characteristics and outcome of pediatric onset psychogenic non-epileptic seizures. *3rd International Conference on Functional (Psychogenic) Neurological Disorders: Abstracts 2017*.

Hansen AS, Mikkelsen MB, Stenager E, Stenager E, Binzer M, Stone J. Functional neurological symptoms and the positive diagnostic process. *Danish Medical Journal* 2018; 180: 1-5.

Hansen AS, Rask CU, Christensen J, Pristed SG, Nielsen RE. Pediatric Onset Psychogenic Nonepileptic Seizures: Establishment of a Danish Nationwide Cohort and a Description of Clinical Characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry* 2019; 58: 47.

Rask CU, Mikkelsen MB, Toscano L, Frostholt L, Hansen, AS. Development of Easily Accessible Information Material for Children and Adolescents with

Psychogenic Nonepileptic Seizures. *Journal of the American Academy of Child and Adolescent Psychiatry* 2019; 58: 48.

Hansen AS, Nielsen RE, Christensen J, Stone J, Rask CU. Stigma Surrounding Functional Seizures. *Pediatric Res* 2020; 88: 684-685.

Supervisor activities:

- May 2018: Co-supervisor on a master thesis for two students of psychology at Aalborg University covering the topic “PNES “.
- Nov 2018: Co-supervisor on a master thesis for a student of medicine at Aarhus University covering the topic “Hyperventilation in PNES“.
- Nov 2019: Co-supervisor on a master thesis for a student of medicine at Aarhus University covering the topic “Quality of life in PNES“.

Other knowledge dissemination activities:

- 2018 – current: Project manager and author of patient information project funded by Trygfonden. The aim of the project is to develop up-to-date and easily accessible information material for children and adolescents with PNES, their families and health professionals. A webpage containing evidence-based information on PNES has been developed and a children’s booklet is in progress and expected to be published in the beginning of 2021.

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Anne Sofie Hansen, October 2020

ARTICLES OF THE DISSERTATION

Paper I

Hansen AS, Rask CU, Rodrigo-Domingo M, Pristed SG, Christensen J, Nielsen RE. Incidence rates and characteristics of pediatric onset psychogenic nonepileptic seizures. *Pediatric Research* 2020; 88: 796-803.

The paper is published and has been made available to the assessment committee.

Paper II

Hansen AS, Rask CU, Christensen A-E, Rodrigo-Domingo M, Christensen J, Nielsen RE. Psychiatric disorders in children and adolescents with psychogenic nonepileptic seizures (PNES): a nationwide matched cohort study.

The paper has been submitted and has been made available to the assessment committee.

Paper III

Hansen AS, Rask CU, Christensen A-E, Christensen J, Nielsen RE. Hospital utilization in childhood-onset psychogenic nonepileptic seizures.

The paper is in preparation and has been made available to the assessment committee.

ENGLISH SUMMARY

Background

A diagnosis of psychogenic nonepileptic seizures (PNES) should be considered, when evaluating children and adolescents presenting with seizure symptoms. PNES are commonly encountered in paediatric and neurological departments, and around 10% of patients presenting with seizures are expected to have PNES. PNES can present with symptoms that mimic epilepsy, and the diagnostic process is often challenging which may delay correct diagnosis, and lead to unnecessary clinical examinations and incorrect treatment with antiepileptic drugs. PNES are associated with emotional distress in affected patients and their families as well as impaired daily functioning with school absenteeism and social withdrawal. A burden of increased healthcare and social costs are also reported; still, patients are reportedly often neglected due to lack of relevant treatment options.

In spite of the reported impact associated with PNES, knowledge on PNES in children and adolescents remains limited, as most prior studies have included only small samples of children from highly specialized clinics or were performed on adult populations.

Aim

The overall aim of this PhD project was to utilize the Danish nationwide patient registries to establish a large cohort of children and adolescents with PNES and thereby gain knowledge regarding incidence, characteristics and morbidity of childhood-onset PNES. The aims of the three studies included in the thesis were:

- 1) To establish a cohort of children and adolescents with PNES and describe the presenting incidence rates and clinical characteristics as well as explore possible differences in clinical characteristics between PNES with and without comorbid epilepsy. (Study I)
- 2) To outline the spectrum and risk of psychiatric disorders in paediatric-onset PNES prior to and in the 2 years following their PNES diagnosis, as compared to children and adolescents with epilepsy and children and adolescents with no PNES or epilepsy (termed healthy controls). (Study II)
- 3) To describe the somatic and psychiatric hospital service use in children and adolescents with PNES 2 years before and 2 years after their PNES diagnosis, as compared to children and adolescents with epilepsy and healthy controls. (Study III)

Methods

The PhD project consisted of three studies and was based on data from the Danish national registries and medical record data. Study I was a nationwide retrospective cohort study of 5-17-year-old children and adolescents registered with an ICD-10 diagnosis corresponding to PNES (i.e. F44.5 “Dissociative seizures” and/or R56.8G “Other and unspecified convulsions, non-epileptic seizures”) in the study period 1996-2014. The medical record of each study participant was assessed to validate the PNES

diagnosis based on a rating of diagnostic certainty, and data on clinical characteristics were extracted from the medical records as well. Study II and Study III were performed as nationwide matched cohort studies and the study sample consisted of the PNES cohort established in Study I, and two matched comparison groups of children and adolescents with epilepsy and healthy controls. Study II described the occurrence of psychiatric disorders prior to and during the 2 years following the PNES diagnosis and reported the relative risk of psychiatric disorders as compared to data obtained from the two control groups. Study III described somatic and psychiatric hospital service use in the PNES cohort during a 2-year period before and a 2-year period after the PNES diagnosis as compared to data in the epilepsy control group and the healthy control group. Incidence rates of inpatient admissions, outpatient care and emergency room visits were reported, and the number of inpatient bed days, outpatient visits and emergency room visits was presented.

Results

A total of 386 children and adolescents were included in the PNES cohort between 1996 and 2014. Study I demonstrated markedly increasing incidence rates of paediatric-onset PNES during the study period from 1996 to 2014. The highest incidence rate was observed for 16-year-old females, and comorbid epileptic seizures were present in more than every tenth patient. Differences between PNES with and without comorbid epilepsy were demonstrated, showing a higher occurrence of intellectual disabilities and support in school as well as prolonged time to PNES diagnosis in children and adolescents with comorbid epilepsy. Study II found that compared with matched children and adolescents with epilepsy and healthy controls, children and adolescents with PNES had an increased risk of psychiatric disorders both prior to and in the 2 years following their PNES diagnosis. Childhood-onset PNES were found to be associated with a wide spectrum of different psychiatric disorders. Study III demonstrated an elevated use of hospital services in the 2 years before and 2 years after the PNES diagnosis, as compared to both children and adolescents with epilepsy as well as healthy controls. Among hospital services used, the majority were provided by somatic hospitals, and the main part of children and adolescents with PNES received no psychiatric hospital care after their PNES diagnosis.

Conclusion

The present PhD project is the first study to establish a nationwide validated cohort of children and adolescents with PNES. The findings demonstrate rising incidence rates and high morbidity, in terms of psychiatric disorders and primarily somatic hospital service use, in children and adolescents with PNES. The results highlight a need for planning systematic healthcare pathways with multidisciplinary treatment options to ensure early recognition and proper management of this young group of patients.

DANSK RESUME

Baggrund

Psykogene ikke-epileptiske anfald, også benævnt PNES eller funktionelle anfald, er en lidelse, som bør overvejes, når man vurderer børn og unge med anfaldsfænomener. PNES defineres som en funktionel neurologisk lidelse med anfaldsvise symptomer, der kan minde om epileptiske anfald, men hvor anfaldene ikke skyldes epilepsi eller anden kendt veldefineret fysisk sygdom. PNES ses hyppigt på børneafdelinger, hvor omkring 10% af børn og unge, som undersøges med mistanke om epilepsi, viser sig at have PNES. Det kan være yderst vanskeligt at skelne mellem PNES og epilepsi, og den diagnostiske proces kan derfor være en udfordring. Dette kan forsinke den korrekte PNES-diagnose samt føre til unødvendige medicinske undersøgelser og fejlbehandling med epilepsi-medicin. Det beskrives ofte, at patienterne bliver overset og ikke modtager relevant behandling, hvilket medfører følelsesmæssig belastning for patienterne og deres familie samt et generelt nedsat funktionsniveau med skolefravær og social tilbagetrækning hos barnet eller den unge.

Til trods for disse udfordringer er den eksisterende viden om PNES hos børn og unge begrænset, da langt størstedelen af tidligere studier af PNES enten har inkluderet små grupper af børn og unge fra højt specialiserede klinikker eller har undersøgt PNES hos voksne personer.

Formål

Det overordnede formål med dette ph.d.-projekt var at benytte de danske patientregistre til at etablere en stor landsdækkende kohorte af børn og unge med PNES, og på den baggrund opnå viden om sygdommens forekomst, kliniske karakteristika og sygelighed hos børn og unge. De tre artikler i afhandlingen havde følgende specifikke formål:

- 1) At etablere en kohorte af børn og unge med PNES med henblik på at beskrive forekomsten og de kliniske karakteristika forbundet med PNES, samt undersøge om der ses forskelle i kliniske karakteristika hos børn og unge, som både har PNES og epileptiske anfald. (Studie I)
- 2) At undersøge forekomsten af og risikoen for psykiatriske sygdomme hos børn og unge med PNES henholdsvis før og to år efter PNES-diagnosen blev stillet sammenlignet med børn og unge med epilepsi samt børn og unge uden PNES eller epilepsi (benævnt raske kontroller). (Studie II)
- 3) At beskrive forbruget af somatiske og psykiatriske hospitalskontakter hos børn og unge med PNES henholdsvis to år før og to år efter PNES-diagnosen blev stillet sammenlignet med børn og unge med epilepsi og raske kontroller. (Studie III).

Metode

Ph.d.-projektet er baseret på data fra danske landsdækkende patientregistre samt data fra patientjournaler. Studie I var et landsdækkende kohortestudie af 5-17-årige børn og unge, som var registreret med en ICD-10 diagnosekode for PNES (dvs. F44.5 "Dissociative kramper" og/eller R56.8G "Andre og ikke specificerede kramper, Non-epileptiske anfald") i studieperioden 1996 til 2014. Patientjournalen for hver enkelt

studiedeltager blev gennemgået med henblik på at validere PNES-diagnosen. Data vedrørende kliniske karakteristika blev endvidere udtrukket fra patientjournalerne. Studie II og studie III blev udført som landsdækkende retrospektive matchede kohortestudier. Studiedeltagerne bestod af PNES kohorten fra studie I samt to matchede kontrolgrupper af henholdsvis børn og unge med epilepsi og raske kontroller. Studie II beskrev forekomsten af psykiatiske sygdomme før og to år efter, at PNES-diagnosen blev stillet samt den relative risiko for psykiatrisk sygdom sammenlignet med de to kontrolgrupper. Studie III beskrev forbruget af somatiske og psykiatiske hospitalskontakter to år før og to år efter, at PNES-diagnosen blev stillet sammenlignet med de to kontrolgrupper. Incidensrater for nyopstartede indlæggelser, ambulante forløb og skadestuekontakter blev rapporteret, og det årlige forbrug af sengedage, ambulante besøg og skadestuekontakter blev beskrevet.

Resultater

Der blev i alt inkluderet 386 børn og unge i PNES-kohorten. Studie I viste en markant stigende forekomst af børn og unge, som hvert år blev diagnosticeret med PNES i Danmark svarende til mere end en tidobling i perioden 1996 til 2014. Den højeste forekomst blev observeret for 16-årige piger. Epileptiske anfald blev påvist hos flere end hver tiende patient med PNES. De børn og unge, som både havde PNES og epilepsi, havde højere forekomst af intellektuelle vanskeligheder og iværksat støtte i skolen samt øget forsinkelse af korrekt diagnose sammenlignet med de børn og unge med PNES, som ikke havde epileptiske anfald. Studie II viste, at sammenlignet med de to kontrolgrupper havde børn og unge med PNES en større risiko for psykiatiske sygdomme både før og to år efter, at PNES-diagnosen blev stillet. PNES hos børn og unge var forbundet med et bredt spektrum af forskellige psykiatiske sygdomme. Studie III fandt, at sammenlignet med de to kontrolgrupper havde børn og unge med PNES et større forbrug af kontakter i hospitalsregi i de to år før samt to efter, at PNES-diagnosen blev stillet. Hospitalskontakterne foregik primært på somatiske hospitalsafdelinger, og størstedelen af børn og unge med PNES havde ikke psykiatiske hospitalskontakter efter de havde fået deres PNES-diagnose.

Konklusion

Dette ph.d.-projekt er det første i verden, der har etableret en landsdækkende valideret kohorte af børn og unge med PNES. Resultaterne viser en stigende forekomst af børn og unge, som diagnosticeres med PNES, samt at PNES hos børn og unge er forbundet med en øget sygelighed i form af psykiatrisk sygdom og primært somatiske hospitalskontakter både før og efter PNES-diagnosen. Samlet set understreger dette vigtigheden af at etablere udrednings- og behandlingstilbud i tæt samarbejde mellem de somatiske og psykiatiske afdelinger med henblik på at sikre en integreret tværfaglig indsats for denne unge patientgruppe.

FIGURES AND TABLES

Figures

Figure 1: Aetiological framework of PNES in children and adolescents.

Figure 2: The three studies of the thesis.

Figure 3: Flowchart of the study sample in Study I, II, and III.

Figure 4: Annual incidence rates of paediatric-onset PNES in Denmark during the period 1996-2014.

Figure 5: Incidence rates of paediatric-onset PNES based on age at diagnosis in Denmark for the period 1996-2014.

Figure 6: Prevalent and incident emotional disorder subgroups and neurodevelopmental disorder subgroups in the PNES cohort and their matched epilepsy control group (ES) and matched healthy controls (HCs).

Figure 7: Incidence rates (IRs) of hospital service use in children and adolescents with PNES and their matched control groups, by period before and after the index date.

Figure 8: Somatic ER visits, bed days and outpatient visits in children and adolescents with PNES and their matched control groups, by period before and after the index date.

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Tables

Table 1: ILAE diagnostic levels of certainty for PNES.

Table 2: Adapted version of the ILAE diagnostic levels of certainty for PNES.

Table 3: Prevalent and incident psychiatric disorders in the PNES cohort and their matched epilepsy control group (ES) and healthy controls (HCs).

ABBREVIATIONS

ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorder
AED	antiepileptic drug
CBT	cognitive behavioural treatment
CD	conduct disorder
CI	confidence interval
CRF	case report form
CRS	the civil registration system
CT	computed tomography
DNPR	the Danish national patient register
DPCRR	the Danish psychiatric central research register
DSM	diagnostic and statistical manual
ECG	electrocardiogram
EEG	electroencephalography
ER	emergency room
ES	epilepsy control group
FND	functional neurological disorder
HC	healthy control group
ICD	international classification of diseases

ILAE	international league against epilepsy
IR	incidence rate
IRR	incidence rate ratio
IQR	interquartile range
MRI	magnetic resonance imaging
MUS	medically unexplained symptoms
NEAD	non-epileptic attack disorder
NES	non-epileptic seizures
OCD	obsessive-compulsive disorder
PER	the Danish population education register
PNES	psychogenic nonepileptic seizures
PPV	positive predictive value
PTSD	post-traumatic stress disorder
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SSRD	somatic symptom and related disorder
WHO	world health organization

PREFACE

My first encounter with psychogenic nonepileptic seizures (PNES) took place several years ago, when I was working as a junior doctor at a child and adolescent psychiatric department. I had two teenage girls referred around the same time for assessment of mood disorder symptoms. Both girls also suffered from PNES, but besides being teenage girls and having a diagnosis of PNES, they had very little in common. When assessing their biological, psychological and social characteristics, I found almost no similarities. I was puzzled about the aetiology of PNES based on these two very different profiles, and I began wondering if there was a link between PNES and the two girls' psychiatric features. I asked my senior colleagues about PNES, but no one had much knowledge about the disorder, and when searching the scientific literature, I found that most prior knowledge was based on studies conducted with adult populations or small samples of children.

After having assessed the two girls, I treated both of them for different psychiatric disorders. Along the way, I became more and more intrigued by these psychogenic nonepileptic seizures, which produced massive physical symptoms but had no well-defined medical somatic explanation. During medical school, my curriculum gave me only little insight into functional somatic symptoms, and it puzzled me to experience that the brain and the body could interact in ways not yet medically explained.

I got inspired to do research on childhood-onset PNES, when encountering my supervisor Charlotte Ulrikka Rask at a course on functional disorders in children and adolescents. Together with René Ernst Nielsen and Jakob Christensen, we set out to do a research project based on the establishment of a Danish nationwide cohort of children and adolescents with PNES. My PhD project was launched; its aim being to gain knowledge on the incidence, characteristics and morbidity of childhood PNES. With this knowledge, we aimed to establish a comprehensive clinical profile of children and adolescents with PNES, which could hopefully inform future strategies for management of this challenging disorder.

Alongside my PhD project, I have been part of a project funded by Trygfonden aimed at developing patient information material for children and adolescents with PNES as well as their families and health professionals. As part of this project I have interviewed patients and their families on their experiences of living with PNES. These families describe to be stigmatized, being left in a treatment gap and great lack of relevant treatment. With the knowledge gained in this PhD project and by use of the material developed as part of the Trygfonden project, I hope to increase awareness of PNES and to help bridge the gap between the somatic and psychiatric field regarding this disorder. My hope for the future is to continue doing research in this area and to be able to do so while occupying a clinical position, where I can use my knowledge to offer relevant treatment and care for children and adolescents with PNES.

BACKGROUND

Psychogenic nonepileptic seizures (PNES), also known as functional seizures, are defined as a functional neurological disorder. This chapter will begin with a brief introduction to the concept of functional somatic symptoms and functional disorders in children and adolescents, which will be followed by a more detailed introduction to PNES. A literature review was conducted in order to assess the existing literature on children and adolescents with PNES. The search was performed in three databases and details of the search strategy are described in Appendix A. The literature search overall identified a small number of studies on children and adolescents with PNES. Although the number of studies published on childhood-onset PNES has increased over the past 20 years, many topics related to PNES are covered in detail only in the scientific literature on the adult population with PNES. Reference will be made to the scientific literature describing knowledge on PNES in the adult population when relevant.

1.1. FUNCTIONAL SOMATIC SYMPTOMS

Functional somatic symptoms are defined as physical symptoms that are not fully explained by a well-defined somatic disorder or organic pathology.^{1,2} Terms like medically unexplained symptoms (MUS) and somatoform symptoms have also been used to describe functional somatic symptoms. Symptoms span a spectrum of severity from everyday transient bodily sensations to recurring somatic symptoms, to conditions with chronic and debilitating symptoms defined as functional disorders.¹ Functional disorders can present with many different physical symptoms from all organ body systems, including pain (typically in the form of abdominal pain in children, or for example headache or musculoskeletal pain), fatigue, dizziness, or symptoms mimicking neurological disorders with motor and sensory disturbances.¹ Examples of functional disorders include conditions such as fibromyalgia, chronic pain, irritable bowel syndrome and PNES.

Functional somatic symptoms are commonly encountered among children and adolescents and are reported to be present from early childhood.³ The Danish National Institute of Public Health conducted a survey on self-reported health among 11-15-year-old school children in Denmark, reporting that daily physical symptoms were experienced by around 20% of boys and 30% of girls in 2018.⁴ The occurrence of persistent and impairing functional disorders in children and adolescents is not clearly defined as numbers vary depending on the criteria and definitions used to define the disorders; however, studies suggest a prevalence of around 4-10%.^{2,5-7} Furthermore, an increase in youth presenting with unspecific somatic symptoms in the hospital-based healthcare setting has been reported,⁸ which could indicate a growing occurrence of functional disorders in children and adolescents.

1.2. PSYCHOGENIC NONEPILEPTIC SEIZURES (PNES)

1.2.1. DEFINITION AND DIAGNOSTIC CLASSIFICATION

Paroxysmal disorders in children and adolescents are commonly divided into epileptic and nonepileptic seizures (NES). Examples of NES are conditions as syncope, migraine, night terrors, motor tics or PNES.⁹ PNES are defined as sudden and transient changes of movement, sensation or level of consciousness that can mimic epilepsy, but without any associated ictal electrical discharges in the brain.¹⁰ Regarding the diagnostic classification of PNES, divergence is found in the international diagnostic classification systems. The International Classification of Diseases, Tenth Revision (WHO ICD-10)¹¹ does not list PNES under a single diagnosis. PNES can be classified in the ICD-10 under F44.5 "Dissociative seizures" or under R56.8 "Other and Unspecified Convulsions"; however, a lack of consensus is reported among clinicians and a range of other ICD-10 codes has also been used by clinicians over time when diagnosing PNES.¹² The ICD-10 diagnosis of F44.5 "Dissociative seizures" specifies the semiology as convulsions only and with the existence of a presumed psychological aetiology being part of the criteria. In the forthcoming International Classification of Diseases, 11th Revision (ICD-11)¹³, PNES are classified as "6B60.4 Dissociative neurological symptom disorder, with non-epileptic seizures", and placed alongside the additional functional neurological symptoms in the category of "Dissociative disorders", and separated from the other functional somatic symptoms, which are placed in a category termed "Disorders of Bodily Distress or Bodily Experience". The diagnostic criteria for "6B60.4 Dissociative neurological symptom disorder, with non-epileptic seizures" are based on the absence of consistency with other neurological or psychiatric conditions, and having a prior psychological stressor is no longer a criterion.¹⁴ Thus, the ICD-11 classifies PNES as a diagnosis of exclusion based on lack of consistency with a medical condition. In contrast, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)¹⁵ classifies PNES under the umbrella category of "Somatic Symptom and Related Disorders (SSRD)" as a "Conversion Disorder (Functional Neurological Symptom Disorder)" focusing on the presence of clinical neurological semiology findings typical of the disorder, whereas previous DSM-IV criteria also required the presence of a preceding psychological stressor.¹⁶ It appears that the new diagnostic classifications in both the ICD and DSM are moving away from diagnostic criteria based on conversion theories to a classification based on the neurological presentation of symptoms; still, differences exist regarding whether to lump together or separate PNES from other functional somatic symptom disorders.^{17,18}

1.2.2. TERMINOLOGY

Many different names have been used to describe PNES over the years, and the changing terminology is mirrored in the evolving perspectives on the aetiological

framework underlying PNES. PNES were first described in the medical literature by Jean-Martin Charcot (1825-1893) as hysterical seizures, and Sigmund Freud (1856-1939) later defined the aetiology as a manifestation of experienced psychological trauma, which were converted into seizure-mimicking symptoms.¹⁹⁻²¹ Thus, terms like "pseudoseizures", "hysterical seizures" and "hystero-epilepsy" have been used to describe PNES based on this purely psychogenic framework. In recent decades, a modern conceptual framework has been introduced that integrates the mind and the brain and sees it as a holistic framework,²² with PNES explained by an interaction between biological, psychological and socioenvironmental factors.²³ Advances in clinical neuroscience now focus on the neurobiology of PNES, and this is also reflected in the terminology of PNES.²⁴ The terms "non-epileptic attack disorder (NEAD)" and "functional seizures" have been introduced to better integrate neurobiological factors without forcing an aetiological framework.²⁵ Attention to the stigma associated with the terminology of PNES has been growing, and feelings of being misunderstood and blamed for having seizures have been described by patients and their families.²⁵⁻²⁷ Among parents of children with PNES, a preference for the terms "functional seizures", "nonepileptic events" or "NEAD" has been reported,²⁶ as these terms were considered the least offensive ones. The most offensive labels were "it is all in his or her head", "hysterical seizures" and "psychogenic seizures"²⁶, and other studies have shown that patients and their families were left with feelings of abandonment and not being believed by clinicians, when receiving the diagnosis of PNES.²⁸⁻³⁰

The term PNES is used throughout this thesis because it is a commonly used and acknowledged term in research. Still, as outlined above, it is important to acknowledge that using the term PNES may be problematic, when communicating the diagnosis of PNES. The label "psychogenic" may be perceived as indicating a statement of a purely psychological framework underlying PNES, and it should be considered carefully which term to use when communicating with patients and lay people.

1.2.3. DIAGNOSTIC ASSESSMENT

Identifying PNES in the clinical setting is challenged by difficulty in differentiating PNES from other paroxysmal events. Misdiagnosis and diagnostic delay lasting several years are often reported,^{31,32} potentially leading to inappropriate treatment and iatrogenic harm.^{33,34} Consensus regarding the clinical requirements for a diagnosis of PNES to be established has been lacking; therefore, in 2013, an international consensus group of clinical experts and researchers (the International League Against Epilepsy, ILAE, Nonepileptic Seizures Task Force) published a report describing the minimum requirement for a diagnosis of PNES based on a staged approach to the diagnosis.³⁵ The gold standard for a PNES diagnosis is an ictal video electroencephalography (EEG); however, meeting the gold standard may not be possible due to lack of video EEG availability in the clinic or because patients primarily have seizures outside the clinic. Furthermore, children may have abnormal EEG activity without having

epileptic seizures, and some epileptic seizures may manifest without showing abnormal ictal EEG activity.³⁶ The test result of a video EEG examination cannot stand alone and should be viewed in the context of the patient history and semiological manifestations as outlined in the ILAE criteria for a diagnosis of PNES.³⁵

Table 1. ILAE diagnostic levels of certainty for PNES^a

Diagnostic level	History consistent with PNES	Witnessed event	EEG information
Possible	Yes	By witness or self-report/description	No epileptiform activity in routine or sleep-deprived interictal EEG
Probable	Yes	By clinician who reviewed video recording or in person, showing semiology typical of PNES	No epileptiform activity in routine or sleep-deprived interictal EEG
Clinically established	Yes	By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG	No epileptiform activity in routine or ambulatory ictal EEG during a typical ictus/event in which the semiology would make ictal epileptiform EEG activity expectable during equivalent epileptic seizures
Documented	Yes	By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on video EEG	No epileptiform activity immediately before, during or after ictus captured on ictal video EEG with typical PNES semiology

^a LaFrance WCJ, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia* 2013;54:2005-2018. The table is reproduced with permission from John Wiley and Sons (© 2013 International League Against Epilepsy).

The ILAE diagnostic approach includes patient history, descriptions of seizure semiology and EEG testing, and four levels of certainty are defined based on this information (possible, probable, clinically established and documented PNES)³⁵ (Table 1). The four levels of diagnostic certainty make it possible to diagnose PNES without having an available ictal video EEG test result, and the levels can be used both when communicating the diagnosis to patients and when conducting research. The ILAE criteria are outlined based on evidence gathered from studies on adult populations,³⁵ and it is important to notice that differences may exist regarding children and adolescents with PNES.³⁷ The PNES diagnosis may be more challenging to establish in children and adolescents due to higher rates of comorbid epilepsy as well as differences in PNES semiology with more non-motor manifestations in children than in adults.^{38,39} A future consensus report on the criteria for a diagnosis of PNES in children and adolescents is needed; meanwhile, the ILAE criteria can be

applied while taking into account the possible differences between the paediatric and adult population.

1.2.4. EPIDEMIOLOGY OF PNES

PNES should be considered when evaluating children and adolescents with paroxysmal events, as around 10% of children and adolescents encountered in specialized epilepsy-monitoring units present with PNES.^{40–42} Regarding studies of PNES in the adult population, even higher numbers are reported with a prevalence of up to 20–40% in specialized epilepsy-monitoring units.^{43,44} Only one study has reported the prevalence of PNES in the general population.⁴⁵ The authors proposed a prevalence of PNES based on a calculation using the prevalence of epilepsy and the assumed prevalence of PNES in patients referred to epilepsy centres, reporting an estimated prevalence of 2 to 33 per 100,000 persons.⁴⁵ Likewise, the incidence of PNES has been reported only in a small number of studies. Three prior studies have reported the incidence rate of PNES in adolescents and adults, and two prior studies have reported the incidence rate of PNES in children. Incidence rates in children aged 7–15 years from the UK and Australia have been reported at 0.4 to 0.5 per 100,000 person years.^{46,47} A study from Iceland reported an incidence rate of 1.4 per 100,000 person years for the age group 15–54 years, with the highest incidence rate reported for the age group 15–24 years at 3.4 per 100,000 person years.⁴⁸ Two other studies on adults populations showed incidence rates ranging from 3.0 to 4.9 per 100,000 person years in individuals referred to epilepsy centers.^{49,50} Thus, population-based studies on the occurrence of PNES are scarce, and further studies are warranted.

1.2.5. CHARACTERISTICS AND COMORBIDITY

PNES most commonly onset during young adulthood; still, the seizures have been observed to affect individuals at all ages.^{39,51–56} PNES are reported in children as young as 5 years of age,^{57,58} and studies have also reported onset of PNES in elderly people above 70 years of age.^{56,59,60} Most prior studies reporting age in children and adolescents with PNES are based on children referred to epilepsy-monitoring units and report a mean age ranging from around 12 to 15 years.^{40,57,61–65}

A female preponderance in PNES is observed, and two recent reviews have shown a female representation of around 70% in children and adolescents.^{57,66} A few studies have suggested that the female preponderance is primarily observed in adolescence, whereas a more equal gender distribution exists in younger children (below 12 years of age).^{41,65,67}

Comorbid epileptic seizures are reported in children and adolescents with paediatric-onset PNES, and the proportion of children and adolescents with comorbid epilepsy varies from 12% to 44%,^{31,68–72} with most numbers coming from children recruited at specialized tertiary treatment units.

Comorbid psychiatric disorders are reported in 16% to 100% of children and adolescents with PNES.^{64,67,68,73–75} Especially emotional disorders and adjustment

disorders are common;^{57,76} however, recent studies have suggested the presence of a broad range of psychiatric disorders, including neurodevelopmental disorders.^{64,77–81} Attention has also been brought to learning disabilities and academic difficulties as possible precipitating factors of PNES in children and adolescents.^{57,82} The occurrence of psychopathology has been reported to be higher in adolescents than in children below 13 years of age.⁶⁷ Most knowledge on psychiatric disorders in children and adolescents with PNES is based on small paediatric study samples from highly specialized treatment units or studies conducted on adult populations, and no prior study on children and adolescents with PNES has described the total spectrum of comorbid psychiatric disorders.

1.2.6. AETIOLOGY

Whereas Charcot and Freud focused on a purely psychological aetiology, modern perspectives on PNES describe a complex multifactorial aetiology based on a model of biological, psychological and socioenvironmental factors.^{10,22,83,84} The aetiological factors are categorized into predisposing, precipitating and perpetuating factors, all considered to play an important role in the aetiology of PNES.^{21,85} Predisposing factors could be negative life events, female sex, functional somatic symptoms, learning disabilities, or traumatic brain injury. Precipitating factors or triggers could be traumatic events like bullying, a physical accident, and loss of a close relative or sudden onset of a somatic disease. Perpetuating or maintaining factors could be psychiatric disorders, sustained interpersonal problems, family dysfunction, illness beliefs, or lack of relevant academic support in school.⁸⁶ (Figure 1)

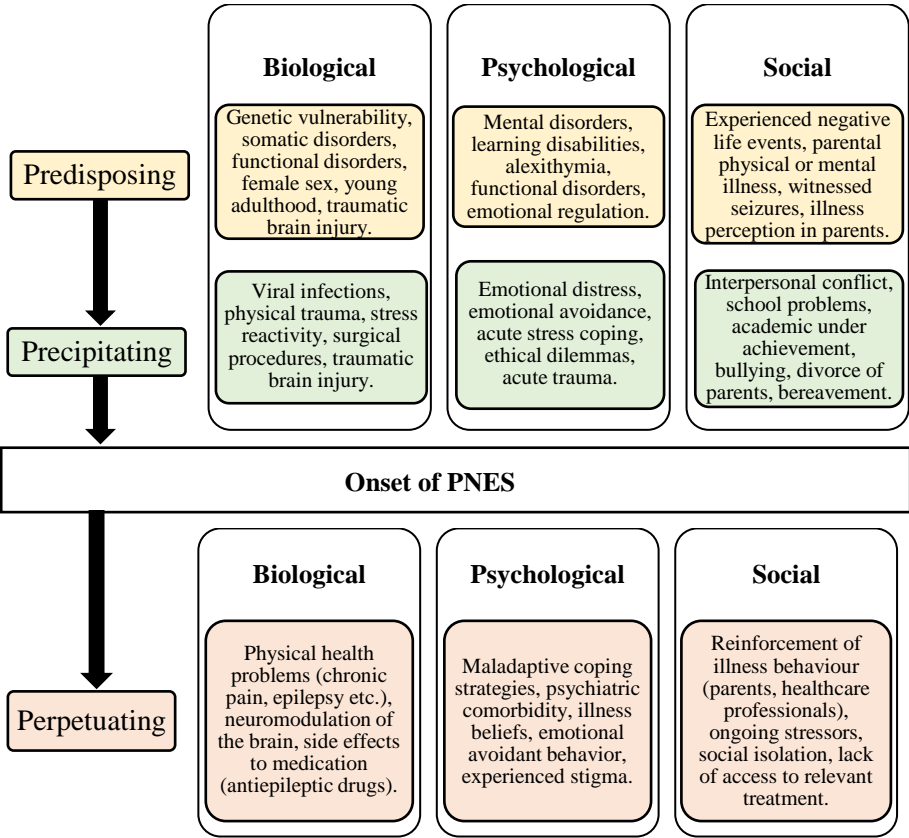
Past years have seen a strong focus on trauma history as a common precipitating characteristic in individuals with PNES. Studies show that adult populations with PNES often have a history of sexual or physical abuse.⁸⁵ However, sexual and physical abuse appears to be less common in children and adolescents with PNES,⁵⁷ whereas school difficulties with bullying and academic difficulties, family discord and interpersonal conflicts are more commonly identified as precipitating factors in childhood-onset PNES.^{57,76}

A growing body of evidence suggests that neurobiological factors may predispose individuals to PNES, and functional neuroimaging studies show pathological findings in patients with PNES and other functional neurological disorders.^{16,24} A “software” and “hardware” analogy has been used as a metaphor to describe that abnormal neurobiological manifestations cause seizures in the context of an intact brain without pathological macroscopic findings; however, emerging evidence suggests that patients with PNES may have both a “software” and a “hardware” problem as structural brain abnormalities may as well be an aetiological factor.⁸⁷

Reuber et al. proposed an “Integrative Cognitive Model (ICM)” as an aetiological model integrating psychological and neurophysiological research;²³ still, a recent ILAE report suggests that it may not be possible to capture the full range of PNES aetiology in a universal model due to the considerable heterogeneity of the disorder.⁸⁸

In total, PNES are described to have a very multifactorial and heterogenic aetiology, and it is necessary to approach the patients with an open mind and consider all possible aetiological factors within a bio-psycho-social framework as part of the assessment as well as when communicating the diagnosis to patients.⁸⁹

Figure 1. Aetiological framework of PNES in children and adolescents^a



^a An aetiological framework demonstrating examples of predisposing, precipitating and perpetuating factors in context of a bio-psycho-social model in children and adolescents with PNES. Inspired by models proposed in Gates and Rowan's Nonepileptic Seizures and Rutter's Child and Adolescent Psychiatry.^{2,90}

1.2.7. IMPACT

As outlined above, PNES are reported to be relatively rare; nevertheless, they impose a considerable burden on patients and their families, the healthcare system as well as the social service system.^{60,91,92}

Children and adolescents and their families describe a great burden of emotional distress associated with PNES and report feelings of confusion, uncertainty and hopelessness.^{29,93} Parents describe profound distress because they experience that clinicians lack knowledge and understanding of functional somatic symptoms, leading to lack of trust and feelings of insecurity.³⁰ Patients with PNES often report uncertainty and insecurity surrounding PNES and feel being doubted by the clinicians, and negative experiences with healthcare professionals are common.⁹⁴

PNES is often associated with impairment of daily functioning including school absenteeism, reduced academic achievement and social difficulties,^{28,57,76} and with parental distress due to loss of work days and disruption of family functioning.^{76,93} Reduced quality of life (QoL) has been reported in studies of adult patients with PNES as compared to patients with epilepsy.⁹⁵ A single study on QoL in a population of adolescents with PNES³⁸ reported a reduced QoL in the adolescents with PNES compared with adolescents without any psychiatric disorder.

PNES have also been observed to be associated with high morbidity, which translates into numerous visits to doctors and emergency rooms, misdiagnosis as epilepsy leading to side effects from antiepileptic drugs (AEDs), and unnecessary medical investigations.^{76,96,97} The diagnostic delay is often up to 3.5 years, and misdiagnosis may lead to lack of relevant treatment and thereby affect the prognosis.⁶⁷ Still, most knowledge on healthcare utilization in PNES is based on studies on adult populations, as studies on children and adolescents are scarce.

1.2.8. TREATMENT AND PROGNOSIS

Multidisciplinary management with close cooperation between physical and mental healthcare is a recommended treatment approach to PNES in children and adolescents.^{57,76} PNES is a disorder at the intersection between somatic and psychiatric care, and continuous involvement of a paediatrician or neurologist after transition to mental healthcare is described as important to help discontinue AEDs when relevant, continue to confirm the accuracy of the PNES diagnosis and assess any new physical symptoms.^{18,76} A combination of psychoeducation and psychotherapy is part of the recommended care, and it is important to communicate the diagnosis to patients and their families in a manner ensuring acceptance of the diagnosis and compliance with treatment.⁹⁸ Several barriers to treatment have been described; one of them being clinicians' attitudes towards the diagnosis.^{86,99} Lack of knowledge about PNES and even an attitude of the seizures being fake are reported among treating clinicians,⁹⁹ and a barrier may also exist due to lack of clinical guidelines and systematic treatment pathways.^{86,100} Another barrier may be the attitude and illness beliefs among patients and their families, and the switch in

diagnosis from an epilepsy diagnosis to a diagnosis of PNES is described as distressing.²⁹ An experience of not being believed or confusion due to uncertainty among doctors has also been reported,²⁸ underlining the importance of careful communication, when delivering the diagnosis of PNES.^{89,101}

Psychological treatment is suggested as an effective intervention in the treatment of functional somatic symptoms;¹⁰² still, limited evidence exists regarding the treatment of children and adolescents with PNES.⁷⁶ A number of observational clinical studies have reported an effect of a multidisciplinary approach integrating mental healthcare with neurological care,^{103–105} showing improved outcomes with regained daily functioning and resumed education. A recent study was the first published randomized controlled trial (RCT) assessing treatment of PNES in children and adolescents; the study used a cognitive behaviourally based approach, showing a reduction of PNES frequency.¹⁰⁶ Cognitive behavioural therapy (CBT) is the most investigated treatment approach in adults;^{16,107,108} however, a Cochrane review outlined that one single treatment approach could not be recommended over another based on the existing evidence, and further RCTs were recommended to increase evidence on the treatment of PNES.^{109,110}

Even though robust evidence on the treatment of PNES in children and adolescents is lacking, two recently published treatment frameworks deserves mentioning. Caplan and colleagues¹¹¹ outlined a management approach based on short- and long-term treatment goals, including individual psychoeducation and psychological treatment with the child, and separate parenting psychoeducation sessions as well as close involvement of the school. Furthermore, Kozłowska and colleagues¹¹² published an outline of a stress-system approach to functional somatic symptoms in children and adolescents and hence provided a framework for treatment based on the existing scientific and clinical research. Both frameworks outline the heterogeneity of children and adolescents with PNES and the need for individualized and flexible treatment plans, and they both present examples of treatment frameworks integrating physical and mental healthcare.

An international consensus guideline on the diagnostic management and treatment of PNES in children and adolescents resting on current evidence and knowledge from clinical experts may improve management of children and adolescents with PNES. A stepped care model defining the management in primary care, the paediatric setting and the child and adolescent psychiatric department could clarify the multidisciplinary healthcare pathway and possibly bridge the treatment gap often experienced by these patients.^{1,100} The prognosis of PNES is reported to be better in children and adolescents than in adults^{113,114} which may be due to earlier recognition thereby avoiding symptom chronicity, reducing severe psychopathology and achieving greater intervention effectiveness.⁵⁷ This difference between young and adult patients with PNES underscores the importance of establishing systematic treatment pathways and early treatment institution in children and adolescents with PNES.

1.3. EPILEPTIC SEIZURES IN CHILDREN AND ADOLESCENTS

As mentioned earlier in this chapter, differentiating between epileptic seizures and PNES in children and adolescents can be challenging. In patients with co-existing PNES and epileptic seizures, this challenge can grow even bigger. Thus, paying attention to the different characteristics of PNES and epilepsy may be critical to the diagnostic process of distinguishing between these two disorders.

A seizure is defined as a transient event characterized by excessive neuronal activity in the brain, and epilepsy is defined as a condition with an imbalance between neuronal excitation in the brain and deficient inhibition leading to a predisposition to recurring seizures.¹¹⁵ Epilepsy was traditionally diagnosed only if the child had a history of two unprovoked seizures with at least 24 hours between the seizures. However, this definition was extended by the ILAE proposing a clinical definition of epilepsy that opens up for establishing the diagnosis based on a single unprovoked seizure with a concurrent probability of recurrent seizures, or establishing the diagnosis based on a defined epilepsy syndrome.^{115,116} Epileptic seizures are divided into different types of seizures (generalized, focal and other types) based on their clinical manifestations and EEG patterns.¹¹⁵ Abnormal seizure activity is typically intermittent and self-limited, stereotyped, lasting seconds to a few minutes and randomly appearing as well as only rarely precipitated by specific triggers; and differences in the presenting semiology may help the clinician distinguish between PNES and epileptic seizures.³⁶ An ictal video EEG recording can be used to assist in establishing a diagnosis of epilepsy; however, interictal EEG testing can be unreliable as up to 5% of children may have epileptiform activity on EEG without having clinical seizures.¹¹⁵

In contrast to PNES, epilepsy has a bimodal incidence curve with the highest incidence occurring in infants and the elderly.^{36,117} The incidence of epilepsy is highest in the first year of life with numbers reported to reach 144 per 100,000 person years, after which the incidence decreases to around 50 per 100,000 person years in childhood and 20 per 100,000 person years in adolescents.^{115,117,118} The gender distribution is overall reported to be equally divided between boys and girls, though with a slightly higher representation of male gender in the age range 10-20 years.^{115,117} Regarding aetiology, epilepsy is divided into a range of aetiological groups: structural, genetic, infectious, metabolic, immune and unknown.¹¹⁹ Furthermore, increasing evidence shows that epilepsy is associated with comorbidities such as psychiatric disorders and learning difficulties, and an association with somatic comorbidities has also been reported.¹¹⁹⁻¹²¹ Epilepsy is considered a disorder associated with high morbidity and mortality which burdens the healthcare system and leads to increased socioeconomic costs.¹²¹⁻¹²³

In summary, since no single clinical characteristic is reported to be pathognomonic of PNES,^{35,124} it is essential to be aware of presenting clinical characteristics that can assist the clinician in distinguishing between PNES and epilepsy to establish the correct diagnosis. Still, only few prior studies have compared children and adolescents

with PNES to children and adolescents with epilepsy, and further research on the clinical features is needed to help clinicians differentiate between PNES and epilepsy.

1.4. SUMMARY OF THE BACKGROUND

In summary, PNES is reported to be a disorder associated with great distress for the affected children and adolescents and their families; moreover, it is a disorder posing a great challenge to the healthcare system. The above literature review shows that most published literature on childhood-onset PNES consists of descriptive case series, case reports, and a small number of case-control studies and systematic reviews. This is defined as an evidence level of 3 to 4,¹²⁵ which corresponds to lower levels of research quality in the hierarchy of evidence. Moreover, most studies include small and highly selected patient populations from specialized tertiary care settings and do not include relevant control groups. Population-based data on the incidence, clinical characteristics and morbidity associated with PNES in children and adolescents are lacking. However, such data could inform the future provision of healthcare to children and adolescents with PNES, facilitate a thorough description of the presenting clinical characteristics and co-morbidity and thereby assist healthcare professionals in the clinical management of the disorder.

The objective of the present PhD project was therefore to achieve an increased understanding of PNES in children and adolescents by utilizing the unique population-based nationwide data gathered in Danish patient registries.

CHAPTER 2. AIMS OF THE THESIS

2.1. OVERALL AIM

The overall aim of this PhD project was to utilize the Danish nationwide patient registries to establish a large cohort of children and adolescents with PNES and thereby gain knowledge regarding incidence, characteristics and morbidity of childhood-onset PNES.

2.2. AIMS OF STUDY I

The aim of this study was threefold: 1) to establish a validated population-based nationwide cohort of children and adolescents with incident PNES included from both secondary and tertiary hospital settings over a period of 2 decades, utilizing data from Danish healthcare registries and medical records; 2) to utilize the established cohort of children and adolescents with PNES to investigate the incidence rate and clinical characteristics of childhood-onset PNES; and 3) to compare clinical characteristics of childhood-onset PNES in children and adolescents with and without coexisting epileptic seizures.

2.3. AIMS OF STUDY II

The aim of the study was to utilize the cohort of children and adolescents with PNES established in Study 1 to outline the spectrum of psychiatric disorders associated with childhood-onset PNES both prior to and 2 years after the PNES diagnosis. Furthermore, the study aimed to assess the risk of psychiatric disorders in children and adolescents with PNES compared to matched children and adolescents with epilepsy and matched children and adolescents with no PNES or epilepsy.

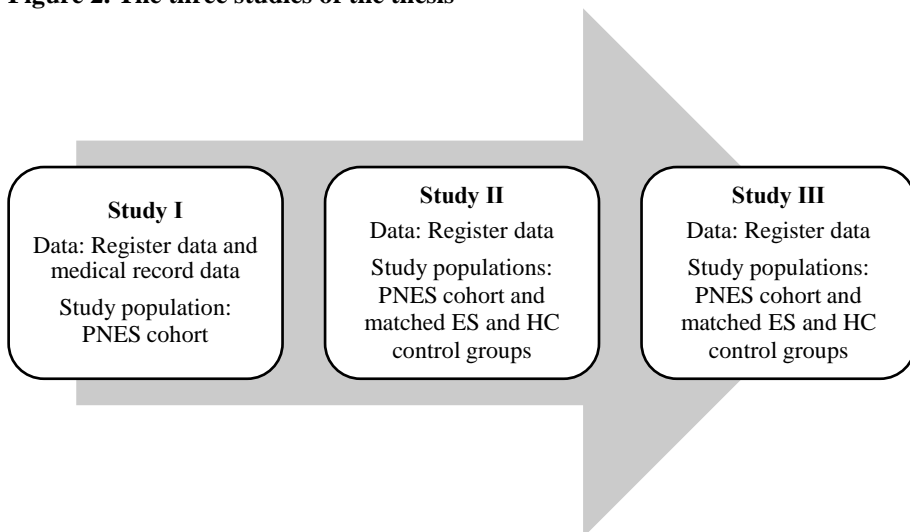
2.4. AIMS OF STUDY III

This study aimed to describe the somatic and psychiatric hospital utilization observed in children and adolescents with PNES 2 years before and 2 years after the diagnosis of PNES. The study aimed to compare the use of hospital services in children and adolescents with PNES to hospital service use observed in children and adolescents with epilepsy and children and adolescents with no PNES or epilepsy.

CHAPTER 3. METHODS

The present thesis is based on three studies linked together by the cohort of children and adolescents with PNES established in Study I (Figure 2). In Study II and Study III, the cohort of children and adolescents with PNES was matched to two control groups consisting of: 1) children and adolescents with epilepsy, and 2) children and adolescents with no PNES or epilepsy. Study I used a combination of register data and data from medical hospital records. Study II and III were based on register data. The below sections will give a presentation of the Danish nationwide registries, which will be followed by an outline of the methods used in each of the three studies.

Figure 2. The three studies of the thesis



Abbreviations: ES: epilepsy; HC: healthy controls.

3.1. THE DANISH NATIONWIDE REGISTRIES

The nationwide population-based registries in Denmark offer an excellent opportunity to perform health-related research. At birth or when immigrating to Denmark, any person is assigned a ten-digit personal identification number (the Civil Person Registration number, CPR). Information on CPR numbers is contained in the Civil Registration System (CRS),¹²⁶ which was established in 1968. The CRS holds information about nationality, sex and date of birth, as well as family relationships

between children and their parents. The CPR number enables linkage of information from a wide range of Danish national registries holding information on healthcare and social services.

Hospital-based care is publicly funded in Denmark, and register-based healthcare data have nationwide coverage of all inpatient, outpatient and acute hospital service use. A number of private hospitals in Denmark also provide somatic and psychiatric healthcare, and the registers contain data on patients treated at both public and private hospitals. Register-based healthcare data are not accessible to the public, but access for research can be obtained following approval from the Danish Health Authority, the Danish Health Data Authority, the Danish Data Protection Agency and Statistics Denmark.

The Danish National Patient Register (DNPR)^{127,128} holds information on in- and outpatient somatic hospital contacts. The DNPR was created in 1977 and initially contained information on inpatient hospital care; information on outpatient hospital care and emergency room visits was added from 1995.

The Danish Psychiatric Central Research Register (DPCRR)¹²⁹ covers data on psychiatric inpatient hospital care from 1970; information on outpatient hospital care and emergency room visits was added from 1995. As from 1995, the DPCRR was integrated into the DNPR.

The Danish Population Education Register (PER)¹³⁰ includes data on all individuals attending education in Denmark. The PER records data on type of education and highest achieved educational level. Information on highest parental educational level for each individual can also be retrieved.

3.2. STUDY I

*(This study was performed in collaboration with Charlotte U. Rask, Maria Rodrigo-Domingo, Sofie G. Pristed, Jakob Christensen and René E. Nielsen. "Incidence rates and characteristics of pediatric onset psychogenic nonepileptic seizures". *Pediatric Research* 2020; 88:796-803).*

3.2.1. DESIGN AND DATA

This study was conducted as a nationwide population-based retrospective cohort study of paediatric-onset PNES in Denmark during the study period 1 January, 1996 to 31 December, 2014.¹³¹

The study was based on data from the CRS, the DNPR, and the DPCRR as well as medical record data from hospital departments across Denmark. Data from the DNPR and the DPCRR were retrieved from the Danish Health Data Authority and utilized to include the study participants as described below, and medical record data were retrieved from the hospital departments and used to validate the diagnosis of PNES for each included individual.¹³¹

3.2.2. STUDY SAMPLE

The use of register diagnoses of PNES is challenged by the lack of consensus among clinicians regarding which ICD-10 diagnosis defines PNES.^{11,12} In order to identify a cohort of children and adolescents with incident PNES, we had to decide which register diagnoses to include. To determine which ICD-10 diagnoses would most likely represent paediatric PNES cases, we consulted a panel of neuropaediatric experts in Denmark. Drawing on their knowledge, we chose to identify all children and adolescents aged 5-17 years (both included) registered in the DNPR with a diagnosis of “Dissociative Seizures” (ICD-10; F44.5) or “Other and Unspecified Convulsions, Non-Epileptic Seizures” (ICD-10; R56.8G) during the period 1996-2014 (both included). In Denmark, the diagnosis of Dissociative Seizures was introduced in 1995 when the ICD-10 was introduced, whereas the diagnosis of R56.8G was introduced in 2010 as a register diagnosis to cover non-epileptic seizures.

The study participants were included at the time they were first given a F44.5 or R56.8G diagnosis. If they were registered with both inclusion diagnoses, they were included at the time they received the first F.445 diagnosis, since we expected this diagnosis to have the highest specificity to represent PNES cases. To ensure inclusion at PNES onset, we excluded participants, who prior to the study period were registered with other register diagnoses possibly representing PNES (ICD-8; 300, 305, 306, 307, 308, 780 and/or ICD-10; F44.5, F91.8, F98.9, R56.8). These register diagnoses were chosen based on advice from a panel of Danish neuropaediatric experts and a Danish study on diagnostic practice of PNES in the paediatric setting.¹² Participants solely registered with an F44.5 and/or R56.8G diagnosis at an emergency department were excluded to increase consistency of the medical record data as the clinical information was expected to be insufficient to validate the PNES diagnosis.

We aimed to retrieve the medical record of every participant identified in the registries using the criteria described above. Medical record data were collected with the purpose of validating the diagnosis of PNES and describe baseline clinical characteristics. Thus, the discharging hospital department that registered the inclusion diagnosis was identified by using each participant’s CPR number. Medical records were collected from 48 hospital departments covering every region in Denmark. Collected information included data on medical admission, progress and discharge notes from the hospital contacts, and results of the following tests if conducted: EEG, magnetic resonance imaging (MRI) or computer tomography (CT) scans of the brain, electrocardiography (ECG) and blood screening results. A case report form (CRF) was developed in collaboration with a consultant neurologist (co-author JC), a consultant child and adolescent psychiatrist (co-author CUR) and an adult psychiatrist (co-author REN). The CRF contained a rating scale to be used when validating the PNES diagnosis and a data inventory of clinical variables to be obtained from the medical records (see Appendix B). We tested the CRF in a subsample of 50 patients from the study population to ensure its usability. Study data were collected and

managed using REDCap electronic data capture tools hosted at The Northern Denmark Region.¹³²

To validate each participant's PNES diagnosis, we used an adapted version of the criteria for diagnostic level of certainty for PNES outlined by the ILAE.³⁵ The ILAE criteria define the diagnostic level of certainty for PNES based on patient history characteristics, witnessed seizure semiology and EEG results. These criteria are considered the golden standard, when assessing a patient for a PNES diagnosis. We chose to adapt the ILAE criteria regarding the EEG data based on pragmatic considerations, since accessibility to EEG testing varied across the hospital settings in Denmark and differed over the study period. In our adapted rating scale, we focused on patient history and witnessed seizure semiology (Table 2). Presence of an ictal video EEG result was necessary to achieve the highest level of diagnostic certainty ("Documented"), whereas the three lower levels ("Clinically Established", "Probable", and "Possible – likely yes") could be rated based on an ictal- or interictal EEG without epileptiform activity as well as without an EEG result (either missing data or not performed). This adaption of our abridged rating scale allowed a patient history consistent with PNES and witnessed seizure semiology consistent with PNES to be sufficient for a diagnosis of PNES without having an ictal EEG result available. Each included participant was rated according to the adapted ILAE criteria and placed in one of the following categories: "Documented", "Clinically established", "Probable", "Possible – likely yes", "Possible - likely no", "Not PNES", "Insufficient information to perform rating". A participant was evaluated as a "Confirmed case" if rated: "Documented", "Clinically established", "Probable" or "Possible – likely yes". A participant was evaluated as a "Not confirmed case" if rated: "Possible – likely no", "Not PNES" or "Insufficient information to perform rating".

The rating was performed by the primary investigator (the PhD candidate, ASH), a medical doctor with 4 years of broad clinical experience from the somatic field and 4 years of clinical experience from working in child and adolescent psychiatry. The rating process was initiated with a consensus rating between ASH and two co-raters; an experienced consultant child and adolescent psychiatrist (co-author CUR) and an experienced consultant neurologist (co-author JC). In addition, a subsample of cases was assessed by the two co-raters, to ensure that assessments performed by ASH were reliable.

The patients were also evaluated for co-morbid epileptic seizures based on having an EEG showing epileptiform activity in addition to clinical information from the medical record confirming an epileptic disorder. A condition of PNES with co-morbid epileptic seizures was termed "mixed PNES", and a condition of PNES without co-morbid epileptic seizures was termed "pure PNES". An assessment of whether the full criteria for a diagnosis of "Dissociative Seizures" (ICD-10; F44.5) and a diagnosis of "Conversion Disorder; Functional Neurological Symptom Disorder" (DSM-V; 300.11) were fulfilled, was conducted for each participant as well.

Table 2. Adapted version of the ILAE diagnostic levels of certainty for PNES
(Hansen *et al.*, 2020)¹³¹

History: consistent with PNES (Yes/No)	
Witnessed event:	<ul style="list-style-type: none"> A. By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on video EEG B. By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG C. By clinician who reviewed video recording or in person, showing semiology typical of PNES D. By witness or self-report/description
EEG:	<ul style="list-style-type: none"> A. No epileptiform activity immediately before, during or after ictus captured on ictal video EEG with typical PNES semiology B. No epileptiform activity in routine or ambulatory ictal EEG during a typical ictus/event in which the semiology would make ictal epileptiform EEG activity expectable during equivalent epileptic seizures. C. No epileptiform activity in routine or sleep-deprived interictal EEG

Diagnostic level:	History:	Witnessed event:	EEG:
Documented	Yes	A	A
Clinically established	Yes	B	B, C, Not performed, Missing
Probable	Yes	C	B, C, Not performed, Missing
Possible - likely yes	Yes	D	B, C, Not performed, Missing
Possible - likely no	No	D	B, C, Not performed, Missing
Not PNES	No	No	B, C, Not performed, Missing
Insufficient information to perform rating (II)	II	II	II

Conclusion on the case assessment:

PNES case status	Rated adapted diagnostic level
Confirmed case	Documented, Clinically established, Probable, Possible – likely yes
Not confirmed case	Possible – likely no, Not PNES, Insufficient information to perform rating

3.2.3. OUTCOMES

Incidence rates (IRs) of PNES were defined as the annual number of individuals aged 5-17 years (both included) with a validated PNES diagnosis according to above criteria divided by the annual number of individuals aged 5-17 years (both included) in the general population during the period 1996-2014.

The clinical characteristics extracted by use of the CRF were defined based on a review of existing literature on PNES in children and adolescents.^{9,35,57,76} The clinical characteristics included: clinical examinations, hospital information, seizure characteristics, seizure semiology, history of illness, prior treatment, level of functioning, family characteristics and negative life events. Negative life events experienced prior to the diagnosis of PNES were identified based on selected sub-items from the Childhood Traumatic Events Scale¹³³ and the Adverse Childhood Experiences International Questionnaire (ACE-IQ)¹³⁴. Details on the outcome measures on clinical characteristics are outlined in Appendix C.

3.2.4. STATISTICAL ANALYSES

Initially, we conducted descriptive analyses on clinical data from the validated cases. Age was summarized by the median and range, and categorical variables were presented as frequencies and percentages. IRs were calculated based on data from Statistics Denmark covering the annual number of individuals between 5-17 years of age in the period 1996-2014 (both included). In years where the number of PNES cases was above 0 but below 3, the number of cases was automatically set to 3 due to data protection rules in Denmark. Data on seizure characteristics, seizure semiology and negative life events were presented in bar charts. Group comparisons were conducted regarding: pure PNES vs mixed PNES, age at PNES diagnosis (divided into “<12 years of age” and “≥12 years of age”) and sex. Chi-squared tests or Wilcoxon rank-sum tests were used for group comparisons.

To assess the inter-rater reliability of the diagnostic rating a random subsample was drawn allowing the study to be able to detect a Cohen’s kappa-coefficient (K) of 0.7-0.8 with a power of 80%. Based on the pilot testing of 50 cases performed by ASH, the raters were assumed to identify cases as positive for PNES in minimum 50% of the cases. To reject the null hypothesis (K=0.4) with a significance level of 0.05, 9-22 patients would be needed.¹³⁵ Thus, two random subsamples of 30 cases were assessed for the inter-rater agreement having the two co-raters assess 30 cases each. Inter-rater reliability was assessed with un-weighted kappas as to whether the raters evaluated the case “Confirmed” or “Not confirmed”.¹³⁶ The un-weighted kappa coefficients were calculated between the primary rater and the two co-raters separately. Statistical analyses were performed using Stata15. The level of significance was set at 0.05.

3.2.5. ETHICS

The study was approved by the Danish Data Protection Agency, the Danish Health Data Authority and the Danish Health Authority. Patient consent was not required according to Danish law. The head of each clinical hospital department gave permission to retrieve medical record data.

3.3. STUDY II

(This study was performed in collaboration with Charlotte U. Rask, Ann-Eva Christensen, Maria Rodrigo-Domingo, Jakob Christensen and René E. Nielsen. Article submitted).

3.3.1. DESIGN AND DATA

Study II was conducted as a nationwide population-based retrospective matched cohort study of psychiatric comorbidity in children and adolescents with PNES. The Danish PNES cohort established in Study I during the inclusion period between 1 January, 1996 and 31 December, 2014 was matched with two comparison groups: 1) a group of children and adolescents with epilepsy (ES), and 2) a group of children and adolescents with no PNES or epilepsy (termed healthy controls, HC).¹³⁷

The study was based on data from four Danish registries: the CRS, the DNPR, the DPCRR and the PER. The CPR numbers of the individuals in the PNES cohort were uploaded to Statistics Denmark, and linked to the Danish nationwide register data.¹³⁷

3.3.2. STUDY SAMPLE

The validated PNES cohort established in Study I defined the PNES study participants in Study II, and we included every individual from the PNES cohort for whom register data were available. For further details on the establishment of the PNES cohort, see the detailed description above under the methods section of Study I. For each individual in the PNES cohort, we used the CRS, the DNPR and the DPCRR to identify two matched comparison groups as described in the following sections. The sampling of the two comparison groups was done without replacement; thus individuals in each comparison group could not act as a comparison subject to more than one PNES case.

We included a comparison group consisting of children and adolescents registered with a diagnosis of epilepsy (ICD-10: G40.x) during the inclusion period matched 3:1 to the PNES cases on sex, year of birth and year of inclusion diagnosis. The index date was set as the initial date of the incident hospital contact with the registered

inclusion diagnosis of epilepsy. To ensure that we included only incident cases with epilepsy, children and adolescents with a diagnosis of epilepsy (ICD-8: 345; ICD-10: G40.x) prior to the inclusion period were excluded. Furthermore, individuals with a diagnosis of PNES (ICD-8: 300, 305, 306, 307; ICD-10: F44.5, R56.8G) prior to their index date were also excluded from the epilepsy controls.

The healthy controls were children and adolescents from the general population matched 5:1 to the PNES cases on sex and year of birth. Individuals with a diagnosis of PNES (ICD-8: 300, 305, 306, 307; ICD-10: F44.5, R56.8G) and/or a diagnosis of epilepsy (ICD-8: 345; ICD-10: G40.x) prior to the corresponding index date of the matched PNES case were not eligible for inclusion in the HC group.

3.3.3. OUTCOMES

Psychiatric diagnoses registered prior to the index date were grouped into diagnostic categories as described below and named “prevalent psychiatric disorders”. Psychiatric diagnoses registered within 2 years after the index date were grouped similarly and named “incident psychiatric disorders” when the individual had no registered prevalent psychiatric disorder within the diagnostic category. Individuals with multiple psychiatric disorders were included in the analyses of each corresponding diagnostic category.¹³⁷

Based on previous studies in PNES,^{57,76,88,138} we categorised the registered psychiatric diagnoses in as follows: “Emotional disorders” (i.e. anxiety, obsessive-compulsive disorder (OCD) and mood disorders (ICD-10: F30-F39, F40-F42, F93, F98 (excluding F98.8C))), “Adjustment disorders” (i.e. stress-related conditions, post-traumatic stress disorder (PTSD) and attachment disorders (ICD-10: F43, F94)), “Neurodevelopmental disorders” (i.e. attention hyperactivity deficit disorder (ADHD/ADD), autism spectrum disorder (ASD), tics/Tourette’s syndrome and conduct disorder (CD) (ICD-10: F84, F88-F89, F90-F92, F95, F98.8C)), “Intellectual disorders” (ICD-10: F70-F79, F80-F83), “Somatic symptom and related disorders” (ICD-10: F44 (excluding F44.5), F45, F48), “Personality disorders” (ICD-10: F60-F61), “Psychotic disorders” (ICD-10: F20-F29), “Eating disorders” (ICD-10: F50), “Self-harm” (ICD-10: X60-X84) and “Substance use” (F10-F19) (see Appendix D).¹³⁷

Two further outcomes were defined for both prevalent and incident psychiatric disorders: “Any psychiatric disorder” was a binary variable identifying the occurrence of any of the above defined psychiatric disorder categories in an individual, and “Two or more psychiatric disorders” was a binary variable identifying the occurrence of two or more of the above defined psychiatric disorder categories in an individual. Additionally, we investigated diagnostic subgroups for two diagnostic categories: emotional disorders (i.e. anxiety disorders, mood disorders, and OCD) and neurodevelopmental disorders (i.e. ADHD/ADD, ASD, CD and tics/Tourettes syndrome) (see Appendix D).¹³⁷

The following covariates were defined:

“Any prevalent psychiatric disorder” was defined as a binary variable determined by the prevalence of “Any psychiatric disorder” prior to the index date as defined above.

“Parental history of psychiatric disorders” was defined as a binary variable determined by registration of “Any psychiatric disorder” prior to the index date in either of the parents of the included children and adolescents. “Parents’ highest level of education” was defined as the highest registered completed level of education at the index date for either of the individual’s parents and divided into four levels: primary (elementary school), secondary (high school), vocational (skilled) and college (short-, medium- and long-term education).¹³⁷

3.3.4. STATISTICAL ANALYSES

Continuous variables were summarized by median and interquartile range, while categorical variables were presented as frequencies and percentages. For each of the outcomes listed above, Poisson regression with robust estimation of standard error was used to compute relative risks (RRs) of psychiatric disorders with PNES as the reference group.¹³⁹ We calculated both crude and adjusted RRs with corresponding 95% CIs and reported inverted RRs and CIs for a more intuitive interpretation. For “Prevalent psychiatric disorders”, the models were adjusted for “Parental history of psychiatric disorders” and “Parents’ highest level of education”. For “Incident psychiatric disorders”, the models were adjusted for “Any prevalent psychiatric disorder”, “Parental history of psychiatric disorders” and “Parents’ highest level of education”. A Wald test was used for comparison of all three groups.

Sensitivity analyses performed included sex-stratified analyses and analyses of subpopulations consisting of children and adolescents from the PNES population with 1) no comorbid epileptic seizures, 2) video EEG validation of the PNES diagnosis, and 3) children above 12 years of age at the index date.

Statistical analyses were performed using Stata 16 at Statistics Denmark remote server. Results with p-values below 0.05 were considered statistically significant.

3.3.5. ETHICS

The Danish Data Protection Agency, the Danish Health Data Authority and the Danish Health Authority approved the study and data use. Patient consent was not required according to Danish law.

3.4. STUDY III

(This study was performed in collaboration with Charlotte U. Rask, Ann-Eva Christensen, Jakob Christensen and René E. Nielsen. Article in preparation).

3.4.1. DESIGN AND DATA

Study III was conducted as a nationwide population-based retrospective matched cohort study of hospital utilization in children and adolescents with PNES. The Danish PNES cohort established in Study I during the inclusion period between 1 January, 1996 and 31 December, 2014 was matched with two comparison groups: 1) a group of children and adolescents with epilepsy, and 2) a group of children and adolescents with no PNES or epilepsy (HCs).¹⁴⁰

The study was based on data from the CRS, the DNPR, and the DPCRR. Data on somatic hospital utilization were retrieved from the DNPR, and data on psychiatric hospital utilization were retrieved from the DPCRR.¹⁴⁰

3.4.2. STUDY SAMPLE

The study sample included in Study III was identical to the study sample included in study II, thus consisting of the PNES cohort and a matched comparison group of children and adolescents with epilepsy as well as a matched comparison group of HCs. For further details on the establishment of the PNES cohort and the matched comparison groups, see the detailed description above under the methods section of Study I and Study II.

3.4.3. OUTCOMES

As described in the methods section under Study II, we defined an index date for each individual in the study sample. The index date for PNES cases and ES controls was defined by the date of the inclusion diagnosis (PNES or epilepsy). The index date for the HC group was defined by the index date of their matched PNES case. Furthermore, four periods were defined: 24-13 months before the index date, 12-0 months before the index date, 0-12 months after the index date, and 13-24 months after the index date.

The primary outcome of the study was hospital utilization. Somatic and psychiatric use of hospital services registered 2 years before and 2 years after the index date was identified. Somatic hospital utilization was defined as utilization registered in the DNPR, and psychiatric hospital utilization was defined as utilization registered in the DPCRR.¹⁴⁰

The primary outcome was divided into the following subtypes of hospital service use for both somatic and psychiatric hospital utilization:

“ER visits”: defined as registered emergency room (ER) hospital visits.

“Inpatient admissions”: defined as commenced inpatient hospital admissions.

“Inpatient bed days”: defined as the number of bed days in connection with an inpatient hospitalization. The number of bed days was defined as the number of days between the admission and discharge date of hospitalization.

“Outpatient care”: defined as commenced outpatient hospital care. Additionally, inpatient hospital admissions, with outpatient visits registered as linked to the inpatient admission, was assumed to be incorrectly registered and was defined as outpatient care.

“Outpatient visits”: defined as the number of visits registered in connection with commenced outpatient care.¹⁴⁰

Multiple inpatient hospitalizations may contribute to the number of bed days over a particular period, and a single inpatient hospitalization may contribute to the number of bed days in multiple periods, both instances depending on the date of admission and the date of discharge.

Multiple courses of outpatient care may contribute to the number of outpatient visits in a single period, and a single course of outpatient care may contribute to the number of outpatient visits in multiple periods, depending in both instances on the initial date and the date of completion of outpatient care.¹⁴⁰

3.4.4. STATISTICAL ANALYSES

Characteristics of the study sample were reported with continuous variables summarized by median and interquartile range, and categorical variables were presented as frequencies and percentages.

IRs and their corresponding 95% confidence intervals (CIs) were calculated and graphed at each period for each study group and for each of the following subtypes of commenced hospital service use: ER visits, inpatient admissions and outpatient care for somatic as well as psychiatric hospital utilization. Estimations were carried out using a Poisson regression model with robust standard error and an interaction term between time period and study group, while accounting for censoring due to death or immigration, and with the PNES group at 12-0 months before the index date as reference.¹³⁹ Incidence rate ratios (IRRs), comparing the PNES group to the ES and HC groups, respectively, were calculated for each period based on the aforementioned model and reported as inverted IRRs for readability. A Wald test was used for comparison of all groups for each period.

The number of ER visits, inpatient bed days, and outpatient visits for somatic as well as psychiatric hospital utilization were categorized and visualized as bar graphs for each period and study group.

Sensitivity analyses were performed excluding the following individuals from the PNES population as well as their matched controls: I) children and adolescents with comorbid epileptic seizures, and II) children and adolescents not having a video EEG validated PNES diagnosis. An additional sensitivity analysis was performed excluding the inpatient hospital admissions registered with outpatient visits, assumed to be incorrectly registered outpatient care.

The level of significance was set to 0.05. Statistical analyses were performed using Stata 16 at the Statistics Denmark server with remote access.

3.4.5. **ETHICS**

The Danish Data Protection Agency, the Danish Health Data Authority and the Danish Health Authority approved the study and data use. According to Danish law, patient consent is not required for registry-based studies.

CHAPTER 4. RESULTS

The main results of Study I, Study II and Study III are presented in this chapter. The results are reported as summaries of the findings divided into main themes, and key figures and tables are included from the three articles on which the thesis is based. When relevant, additional details are provided to elaborate on the results reported in the articles.

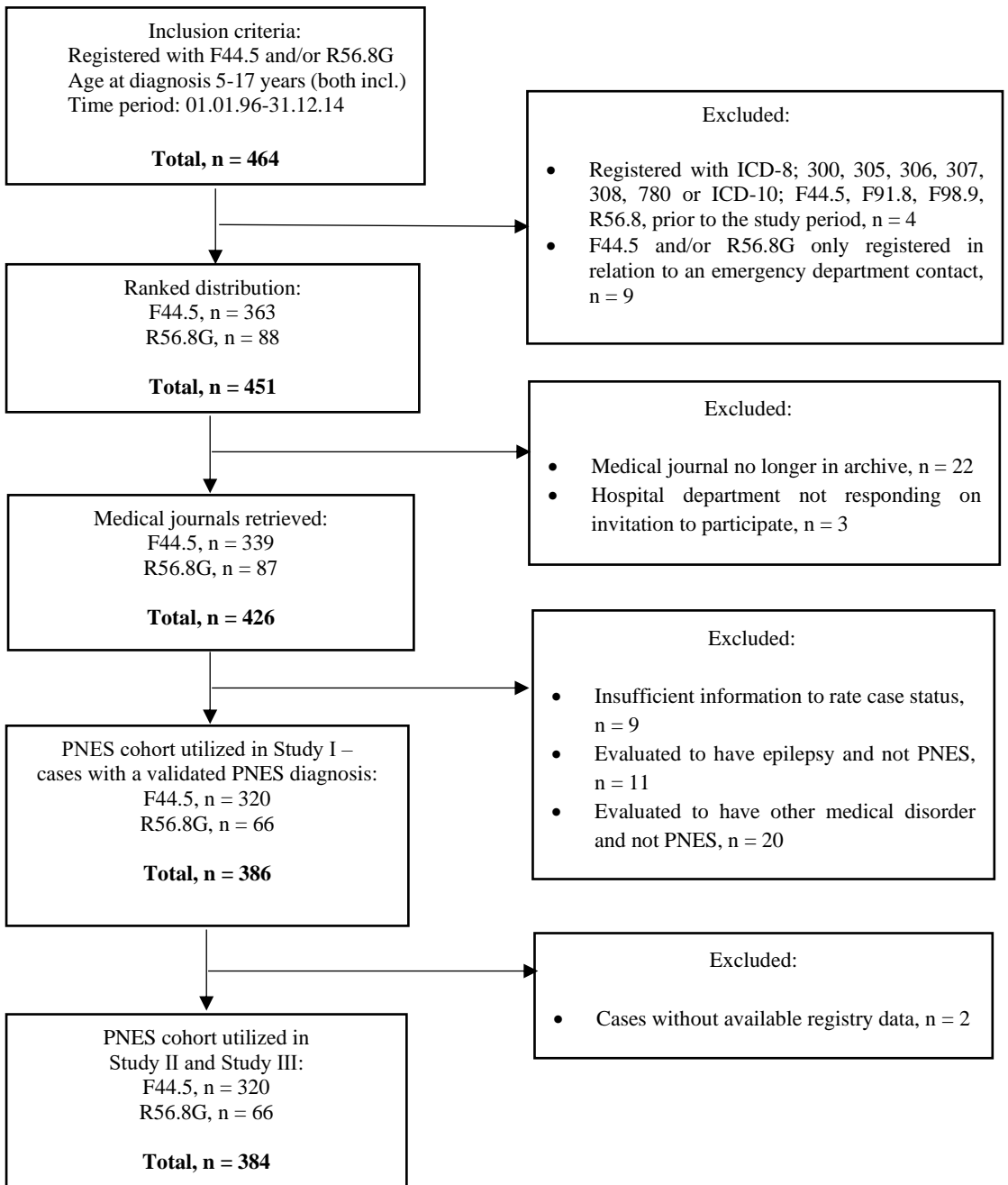
4.1. STUDY I

(This study was performed in collaboration with Charlotte U. Rask, Maria Rodrigo-Domingo, Sofie G. Pristed, Jakob Christensen and René E. Nielsen. "Incidence rates and characteristics of pediatric onset psychogenic nonepileptic seizures". Pediatric Research 2020; 88:796-803).

4.1.1. THE PAEDIATRIC PNES COHORT

We identified 464 participants in the registers with one of the two inclusion diagnoses for PNES (ICD-10: F44.5 and/or R56.8G). After exclusion due to either a prior diagnosis of a possible PNES condition or registration at an emergency department only, 451 participants remained available for collection of medical record data. Medical records were retrieved for 426 participants from 46 different hospital departments covering every region of Denmark, with two departments not consenting to participate in the study. We rated 386 patients as cases and included them in the final PNES study cohort (Figure 3). Children and adolescents in the PNES cohort were recruited from paediatric departments (45.3%), neurology departments (42.5%), child and adolescent psychiatric departments (10.4%) and general medicine departments (1.8%).¹³¹

Figure 3. Flowchart of the study sample in Study I, II, and III (Hansen et al.,2020)¹³¹



4.1.2. CASE RATING

The inter-rater reliability was assessed utilizing two random samples of 30 cases, with the two co-raters rating 30 cases each. There was no significant difference between the sample utilized for the inter-rater reliability assessment and the total study sample regarding female gender ($n = 48$ (80.0%) vs. $n = 309$ (79.0%), $P = .86$), age at inclusion (15.68 vs 15.70 years, $P = .80$), year of diagnosis (June 2011 vs September 2011, $P = .87$) or frequency of ICD-10 F44.5 as inclusion diagnosis ($n = 51$ (85.0%) vs. $n = 312$ (79.8%), $P = .34$). There was agreement between the primary rater and the two co-raters in 100% (rater CUR; Cohen's kappa = 1.0) and 93.3% (rater JC; Cohen's kappa = 0.76) of classifications of participants as PNES cases. This corresponds to an agreement level of almost perfect (Cohen's kappa range: 0.81-1.0) and substantial (Cohen's kappa range: 0.61-0.80). The rated diagnostic levels for the final PNES cohort were: "Documented": $n = 90$ (23.3%), "Clinically Established": $n = 173$ (44.8%), "Probable": $n = 23$ (6.0%) and "Possible – likely yes": $n = 100$ (25.9%). EEG information was retrieved for 336 (87.0%) of the final PNES cases.¹³¹

4.1.3. VALIDITY OF THE REGISTER DIAGNOSES

Regarding the validity of the two inclusion register diagnoses, the positive predictive value (PPV) of a PNES diagnosis was 94.4% for ICD-10 F44.5 and 75.9% for ICD-10 R56.8G. Furthermore, all cases included in the final PNES cohort fulfilled the diagnostic criteria for "Conversion Disorder; Functional Neurological Symptom Disorder" (DSM-V; 300.11), whereas only 199 (51.6%) cases in the final study cohort fulfilled the criteria for the diagnosis of "Dissociative Seizures" (ICD-10; F44.5). This was primarily due to cases not fulfilling one of the specific criteria of ICD-10 F44.5 regarding a prior history of a stressful life event ($n = 164$, 42.5%).¹³¹

4.1.4. INCIDENCE RATES OF PAEDIATRIC-ONSET PNES

The IR of paediatric-onset PNES in Denmark was 2.4 per 100,000 person years during the total study period between 1996 and 2014. However, the IR increased markedly between 2005 and 2014, with the maximum IR of 7.4 per 100,000 person years observed in 2014 (Figure 4). The increase during the study period was observed primarily in females, who presented an IR of 12.0 per 100,000 person years in 2014, while the male IR was 3.1 per 100,000 person years. Regarding the IR for the total study period stratified by age at diagnosis, the highest IR was observed for the 16-year-old adolescents with an IR of 7.9 per 100,000 person years (Figure 5). For the IRs stratified by rated diagnostic level of certainty for PNES, the "Clinically established" PNES cases showed the highest IR with a maximum of 2.7 per 100,000 person years in 2014, followed by an IR of 2.1 per 100,000 person years in the "Possible – likely yes" cases, an IR of 1.8 per 100,000 person years in the "Documented" cases and an IR of 0.8 per 100,000 person years in the "Probable" cases.¹³¹

Figure 4. Annual incidence rates of paediatric-onset PNES in Denmark during the period 1996-2014 (Hansen *et al.*,2020)¹³¹

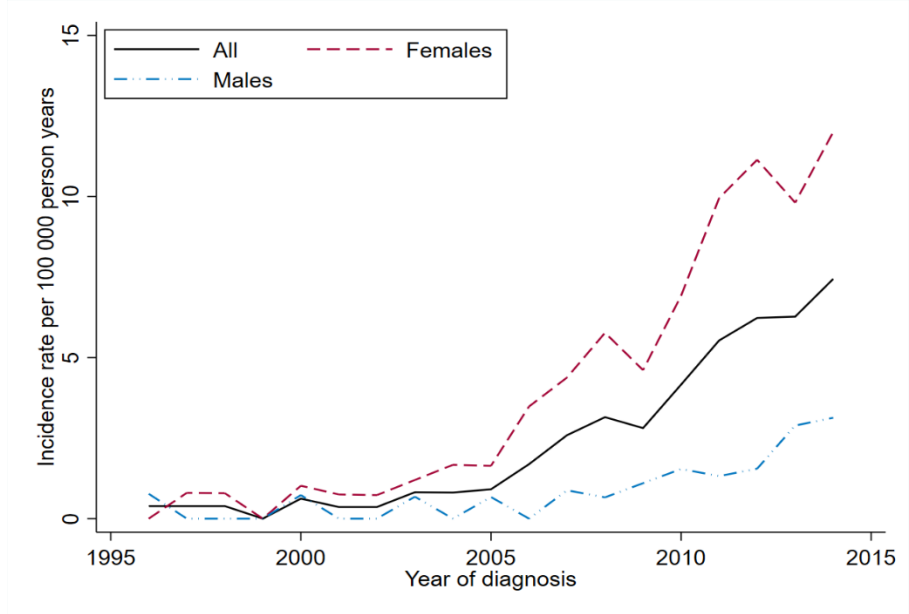
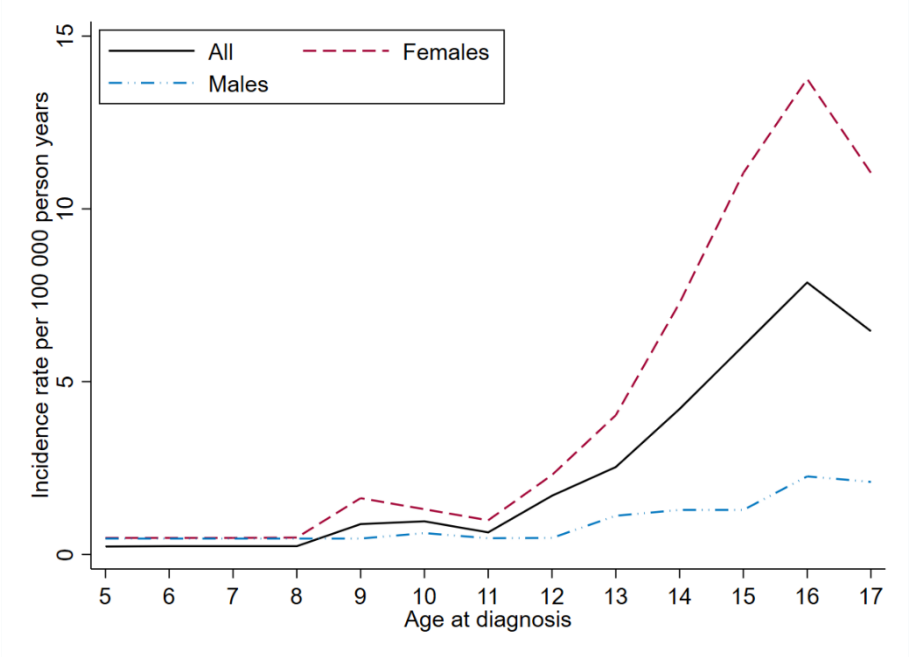


Figure 5. Incidence rates of paediatric-onset PNES based on age at diagnosis in Denmark for the period 1996-2014 (Hansen *et al.*, 2020)¹³¹



4.1.5. CLINICAL CHARACTERISTICS

In the PNES cohort, most of the children and adolescents were females (83.4%) with a median age at diagnosis of 15.7 years. The preponderance of females was lower among children below 12 years of age than among children ≥ 12 years of age (70.3% vs. 84.8%, $P = .02$). A comorbid condition of epilepsy (i.e. mixed PNES) was confirmed in 55 (14.2%) of the validated PNES cases.¹³¹

A prior history of psychiatric disorders was reported in 78 patients (20.2%) and 62 (16.1%) had a history of self-harm behavior. In total, 210 patients (54.4%) reported having experienced a negative life event. In the pure PNES group, school bullying and interpersonal conflicts were the most often reported events, while child neglect and stressful parental divorce were the most common events in the mixed PNES group; still, only the difference in child neglect was statistically significantly different (4.5% vs 14.6%, $P = .004$).¹³¹

Regarding level of functioning, school problems were reported in 133 (34.5%). A total of 105 participants (27.2%) had established support in school, 31 (8.0%) had an intelligence quotient (IQ) below 70 (i.e. mental retardation) and 94 (24.4%) had specific learning difficulties. The mixed PNES group showed a statistically significantly higher proportion of both intellectual disabilities and support in school. Regarding seizure characteristics, the distribution of time from onset of seizures to PNES diagnosis was significantly different between the groups ($P = .03$) with the pure PNES group having a shorter time between onset of seizures and PNES diagnosis (0-6 months). Still, the most common duration from onset of seizures to PNES diagnosis was 0-6 months in both the pure PNES group (43.5%) and mixed PNES group (25.9%). In persons with PNES, seizures were most often reported to happen weekly (pure: 61.5% vs mixed: 50.6%) and the seizures were reported to most often last 5-30 minutes (pure: 61.2% vs mixed: 49.7%).¹³¹

Seizure semiology was overall observed to be very similar for the pure PNES and mixed PNES groups. The most commonly reported seizure semiologies were having a seizure in the presence of others, not having seizures during sleep, having asynchronous movements, having seizures of long duration (i.e. lasting >5 minutes) and having silent seizures. However, some statistically significant differences appeared when we compared the pure PNES and the mixed PNES cases regarding seizure semiology: “Not during sleep” (pure: 258 (78.0%) vs mixed: 36 (65.5%), $P < .05$), “Silent seizures” (pure: 235 (71.0%) vs mixed: 29 (52.7%), $P < .01$), “No incontinence/tongue biting” (pure: 195 (58.9%) vs mixed: 24 (43.6%), $P < .05$), “Emotional features” (pure: 32 (9.7%) vs mixed: 15 (27.3%), $P < .001$) and “Vocalization/ictal crying” (pure: 1 (0.3%) vs mixed: 2 (3.6%), $P < .01$). Furthermore, a lower occurrence of asynchronous movements was observed in the children below 12 years of age than in children ≥ 12 years of age.¹³¹

4.2. STUDY II

(This study was performed in collaboration with Charlotte U. Rask, Ann-Eva Christensen, Maria Rodrigo-Domingo, Jakob Christensen and René E. Nielsen. Article submitted).

4.2.1. THE STUDY SAMPLE

A total of 384 children and adolescents with PNES were included in this study (female proportion: 81.8%, median age at inclusion: 15.7 years (IQR: 14-1-16-8)) (Figure 3). The two matched control groups consisted of 1,152 children and adolescents with epilepsy and 1,920 HCs.¹³⁷

4.2.2. RISK OF PSYCHIATRIC DISORDERS

Among children and adolescents with PNES, 153 (39.8%) had a prevalent psychiatric disorder at the index date, and 150 (39.1%) received an incident psychiatric disorder diagnosis. An elevated risk of “Any psychiatric disorder” was observed in the PNES cases for both prevalent and incident diagnoses as compared with the ES group (prevalent: adjusted RR 1.87 (95% CI: 1.59-2.21), incident: adjusted RR 2.33 (95% CI: 1.92-2.83)) and the HC group (prevalent: adjusted RR: 5.54 (95% CI 4.50-6.81), incident: adjusted RR 8.37 (95% CI: 6.31-11.11)) (Table 3).¹³⁷

4.2.3. SPECTRUM OF PSYCHIATRIC DISORDERS

In the PNES cases, prevalent psychiatric disorders consisted mostly of adjustment disorders (17.5%), SSRDs (12.5%), neurodevelopmental disorders (11.5%), emotional disorders (10.7%) and intellectual disabilities (6.8%). The most frequent incident disorders among PNES cases were adjustment disorders (12.5%), emotional disorders (9.9%), somatic symptom disorders (9.1%), and psychotic disorders (7.4%), followed by neurodevelopmental disorders (6.5%). Comparing the PNES cases with the ES group, we found the highest RRs for prevalent SSRDs (adjusted RR 9.40 (95% CI: 5.31-16.64)), personality disorders (adjusted RR 2.94 (95% CI: 1.17-7.36)) and adjustment disorders (adjusted RR 2.14 (95% CI: 1.60-2.86)); still, the PNES cases showed an elevated risk of nearly all psychiatric disorders categories, only exceptions were a lower risk of psychotic disorders (adjusted RR 0.97 (95% CI: 0.50-1.90)) and substance use (adjusted RR 0.70 (95% CI: 0.31-1.58)). The risk of all incident psychiatric disorders reported was higher among PNES cases than among ES cases. Comparing the PNES cases to the HCs, we observed higher risks for all prevalent and incident psychiatric disorders.¹³⁷

Table 3. Prevalent and incident psychiatric disorders in the PNES cohort and their matched epilepsy control group (ES) and healthy controls (HCs)^a
(Hansen et al., paper submitted)¹³⁷

	PNES (n = 384)	ES (n = 1152)	HC (n = 1920)	P (Wald)
Any prevalent psychiatric disorder	153 (39.8%)	245 (21.3%)	132 (6.9%)	
RR, crude (95% CI)		1.87 (1.59-2.21)	5.80 (4.72-7.12)	< .0001
RR, adjusted* (95% CI)		1.87 (1.59-2.21)	5.54 (4.50-6.81)	< .0001
Any incident psychiatric disorder	150 (39.1%)	174 (15.1%)	72 (3.8%)	
RR, crude (95% CI)		2.59 (2.15-3.11)	10.42 (8.04-13.49)	< .0001
RR, adjusted** (95% CI)		2.33 (1.92-2.83)	8.37 (6.31-11.11)	< .0001

^a Data are presented as number (percentage) unless otherwise indicated. Relative risks (RRs) are presented with corresponding 95% CIs. RRs were calculated with the PNES group as reference and reported as inverted RRs and CIs for a more intuitive interpretation.

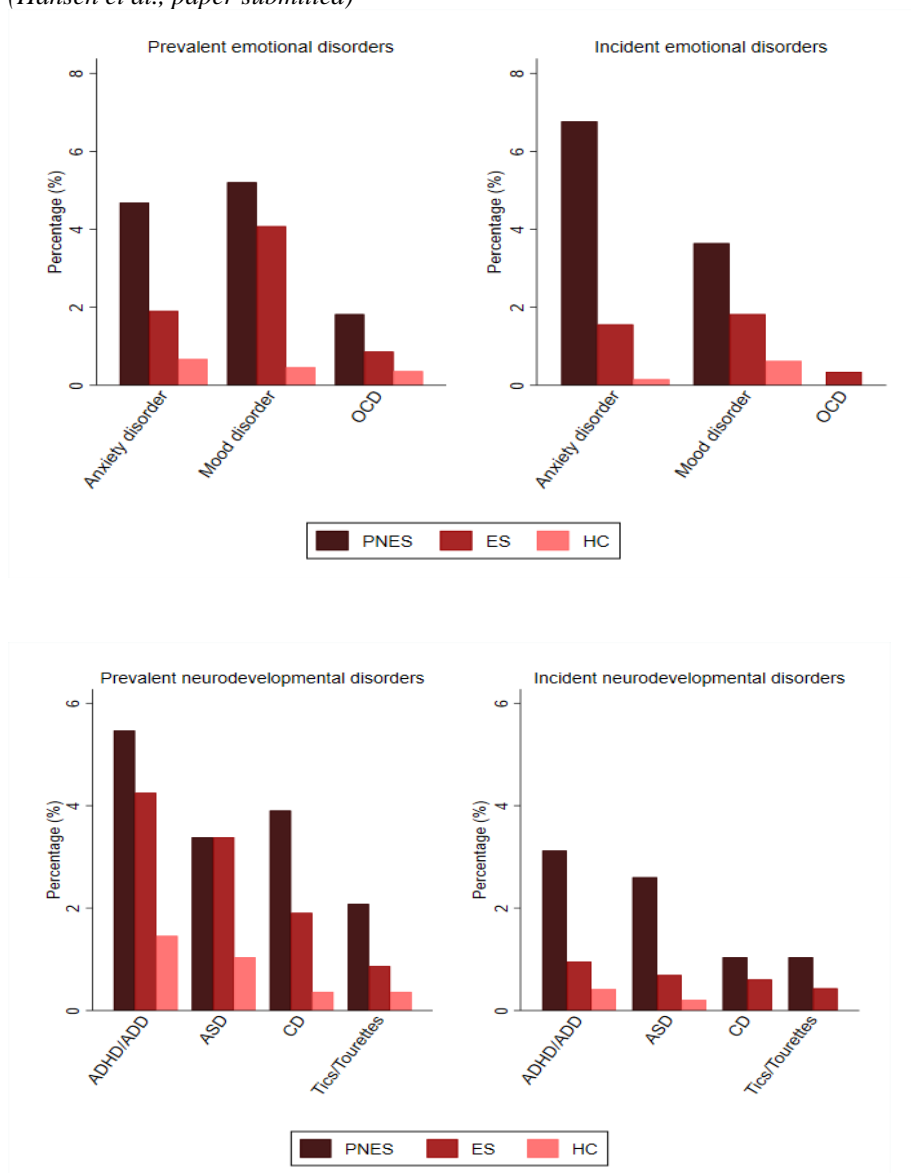
* Adjusted for: Parental history of psychiatric disorders; Parents' highest level of education.

** Adjusted for: Any prevalent psychiatric disorder; Parental history of psychiatric disorders; Parents' highest level of education.

4.2.4. SUBTYPES OF PSYCHIATRIC DISORDERS

Figure 6 illustrates the distribution of subtypes of emotional disorders and neurodevelopmental disorders in the PNES cases and the control groups, respectively. Anxiety disorders and mood disorders were most common in the PNES cases when investigating the emotional disorders category, with anxiety disorders being the most prominent among incident disorders in the PNES cases. Among the neurodevelopmental disorders, attention deficit hyperactivity disorder (ADHD/ADD) was the most common prevalent and incident disorder in the PNES cases.¹³⁷

Figure 6. Prevalent and incident emotional disorder subgroups and neurodevelopmental disorder subgroups in the PNES cohort and their matched epilepsy control group (ES) and matched healthy controls (HCs)
(Hansen et al., paper submitted)¹³⁷



^a Each individual can be represented in more than one of the diagnostic subgroups. Due to data protection rules in Denmark, observations below 3 were not reported.

Abbreviations: OCD: obsessive compulsive disorder; ADHD: attention deficit hyperactivity disorder; ADD: attention deficit disorder; ASD: autism spectrum disorder; CD: conduct disorder.

4.2.5. SENSITIVITY ANALYSES

Sensitivity analyses were conducted on PNES cases with the following characteristics: 1) no coexisting epilepsy (n=330), 2) a video EEG confirmed PNES diagnosis (n=89), and 3) age above 12 years at the index date (n=346). All sensitivity analyses were robust to the study findings showing comparable results regarding the observed occurrence of psychiatric disorders and the calculated RRs for both the prevalent and incident psychiatric disorders. The sex-stratified analyses showed a similar occurrence and distribution of psychiatric disorders among males and females in the PNES population, and the calculated RRs remained comparable as well.¹³⁷

4.3. STUDY III

(This study was performed in collaboration with Charlotte U. Rask, Ann-Eva Christensen, Jakob Christensen and René E. Nielsen. Article in preparation).

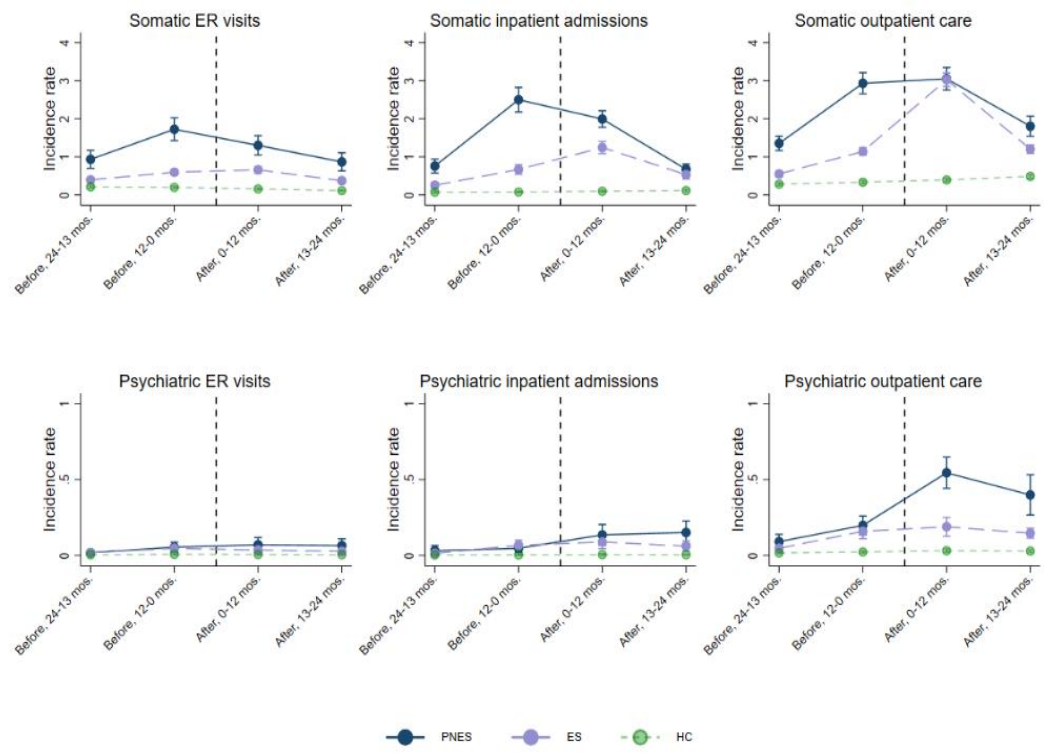
4.3.1. STUDY SAMPLE

A total of 3,456 children and adolescents (PNES cases: n = 384, ES group: n = 1,152, HC group: n = 1,920) were included in the study between 1 January, 1996 and 31 December, 2014, with a median age at inclusion of 15.7 years (IQR: 14.1–16.8) and a female proportion of 81.8%. The PNES cases contributed with full person time in in each period before and after the index date, whereas minimal censoring was present in the ES and HC groups after the index date.¹⁴⁰

4.3.2. HOSPITAL UTILIZATION

In general, the PNES group had a higher level of commenced ER visits, inpatient admissions and outpatient care per person time than the ES and HC group in both the somatic and psychiatric hospital setting (Figure 7). Furthermore, a statistically significant difference in IRRs in each period was observed between the groups. Additionally, a higher number of ER visits, inpatient bed days, and outpatient visits was observed among the PNES cases than among the ES and HC groups for both somatic and psychiatric hospital utilization (Figure 8 and Figure 9).¹⁴⁰

Figure 7. Incidence rates (IRs) of hospital service use in children and adolescents with PNES and their matched control groups, by period before and after the index date^a
(Hansen et al., paper in preparation)¹⁴⁰



^a The vertical dotted line indicates the index date (i.e. date of inclusion diagnosis, or corresponding date for HCs). IRs are presented with corresponding 95% CIs. Due to data protection rules in Denmark, observations above 0 but below 3 were automatically set as “3”.
 Abbreviations: IR: incidence rate; ER: emergency room; mos.: months; PNES: psychogenic non-epileptic seizures; ES: epilepsy; HCs: healthy controls.

4.3.3. SOMATIC HOSPITAL UTILIZATION

The highest IR of somatic hospital utilization among the PNES cases was observed for outpatient care in the period 0-12 months after the index date (IR = 3.05 (95%: CI 2.76–3.35)) with a similar IR in the period 12-0 months before the index date (IR = 2.93 (95%: CI 2.66–3.21)). The highest occurrence of somatic ER visits and inpatient admissions among PNES cases was observed in the period 12-0 months before the index date (ER visits: IR = 1.73 (95%: CI 1.43–2.03); inpatient admissions: IR = 2.50 (95% CI: 2.18–2.83)), and the IRs were observed to decline during the 2 years after the index date to a level comparable to that seen in the period 24-13 months before the index date (ER visits: IR = 0.87 (95%: CI 0.63–1.11); inpatient admissions: IR = 0.68 (95% CI: 0.54–0.81)) (Figure 7). As shown in Figure 8, a high number of somatic ER visits, bed days and outpatient visits were more common in the PNES cases than in the ES and HC groups.¹⁴⁰

4.3.4. PSYCHIATRIC HOSPITAL UTILIZATION

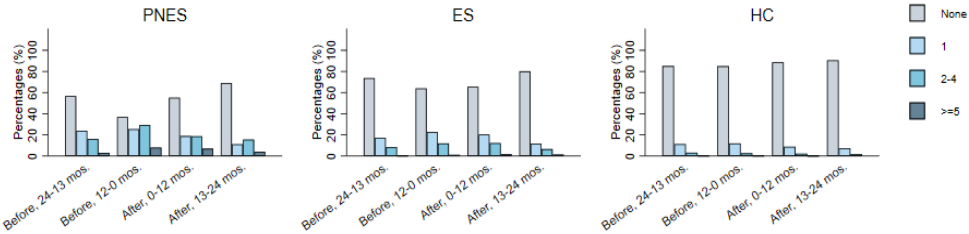
The IRs of psychiatric ER visits and inpatient admissions were generally lower than in IRs presented in the somatic setting for both PNES cases and the ES and HC groups across all periods (Figure 7). The IRs of psychiatric outpatient care were observed to increase after the index date in PNES cases with the highest IRs in the period 0-12 months after the index date (IR = 0.54 (95%: CI 0.44–0.65)). Figure 9 outlines the low occurrence of psychiatric ER visits and bed days in both PNES cases and the matched control groups. In PNES cases, a high number of psychiatric outpatient visits (≥ 10) were most frequent in the period 0–12 months after the index date ($n = 37$ (9.6%)). Among PNES cases, 61.5% had no psychiatric hospital service use in the 2 years after the index date.¹⁴⁰

4.3.5. SENSITIVITY ANALYSES

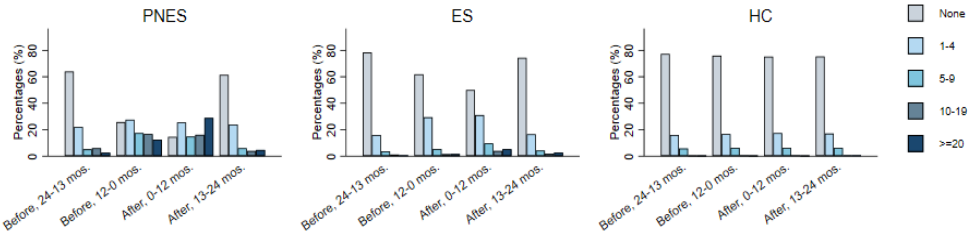
We conducted sensitivity analyses excluding the following children and adolescents from the PNES population: I) children and adolescents with comorbid epileptic seizures ($n = 54$), and II) children and adolescents not having a video EEG validated PNES diagnosis ($n = 295$), as well as their matched controls. A further sensitivity analysis was conducted excluding all inpatient admissions with registered outpatient visits and assumed to be incorrectly registered outpatient care. The sensitivity analyses showed that the results and conclusions of the study remained robust.¹⁴⁰

Figure 8. Somatic ER visits, bed days and outpatient visits in children and adolescents with PNES and their matched control groups, by period before and after the index date^a (Hansen et al., in preparation)¹⁴⁰

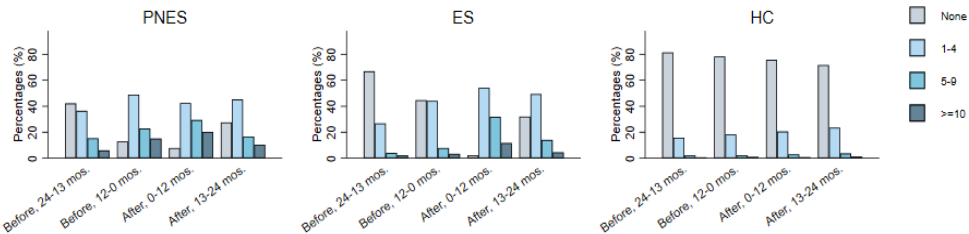
Number of somatic ER visits



Number of somatic inpatient bed days



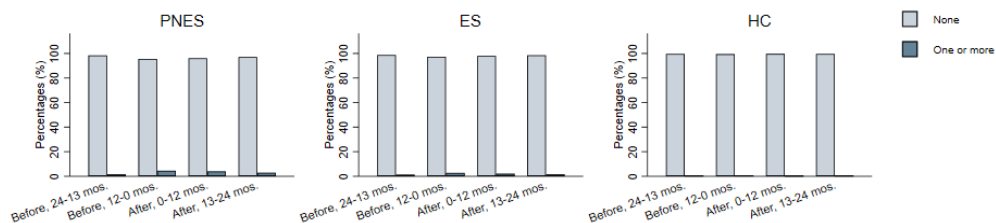
Number of somatic outpatient visits



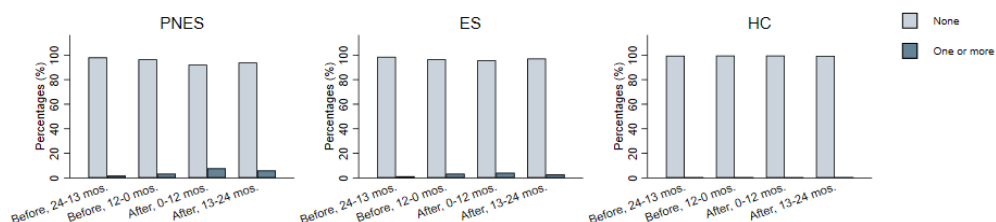
^a The index date was defined by the date of the inclusion diagnosis (PNES or epilepsy) for the PNES and ES group and by the corresponding index date of the matched PNES case in the HCs.
Abbreviations: ER: emergency room; PNES: psychogenic nonepileptic seizures; ES: epilepsy; HC: healthy controls; mos.: months.

Figure 9. Psychiatric ER visits, bed days and outpatient visits in children and adolescents with PNES and their matched control groups, by period before and after the index date^a (Hansen et al., in preparation)¹⁴⁰

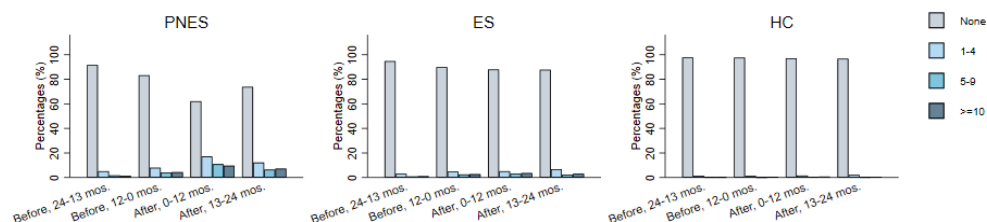
Number of psychiatric ER visits



Number of psychiatric inpatient bed days



Number of psychiatric outpatient visits



^a The index date was defined by the date of the inclusion diagnosis (PNES or epilepsy) for the PNES and ES group and by the corresponding index date of the matched PNES case in the HCs.
Abbreviations: ER: emergency room; PNES: psychogenic nonepileptic seizures; ES: epilepsy; HC: healthy controls; mos.: months.

CHAPTER 5. DISCUSSION

This PhD project is the first nationwide population-based study of paediatric-onset PNES. A large validated cohort of children and adolescents with PNES was established by performing a rigorous retrospective medical chart review covering a period lasting 2 decades. The study included two large comparison groups consisting of children and adolescents with epilepsy and children and adolescents without PNES or epilepsy (termed healthy controls, HCs). The findings show increasing IRs of pediatric-onset PNES during the study period from 1996 to 2014. The highest incidence rate was observed for 16-year-old females, and more than every tenth child and adolescent with PNES had comorbid epileptic seizures. Differences between PNES with and without comorbid epilepsy were demonstrated, showing a higher occurrence of intellectual disabilities, more support in school as well as prolonged time to PNES diagnosis in the children and adolescents with comorbid epilepsy compared with those without epilepsy. We found that compared with children and adolescents with epilepsy and HCs, children and adolescents with PNES had an increased risk of psychiatric disorders both prior to their PNES diagnosis and the first 2 years after their PNES diagnosis. Childhood-onset PNES was found to be associated with a wide spectrum of psychiatric disorders. Finally, the findings demonstrated that children and adolescents with PNES used more hospital services in the 2 years before and 2 years after their PNES diagnosis than children and adolescents with epilepsy and HCs. The main part of hospital services was provided in the somatic hospital setting, and somatic service use was most prevalent in the year preceding the PNES diagnosis. The elevated level of somatic service use persisted after the PNES diagnosis and remained higher than in children and adolescents with epilepsy as well as HCs. The majority of children and adolescents with PNES received no psychiatric hospital care after their PNES diagnosis.

This chapter will discuss the findings of the three studies of the thesis. The findings will be summarized and discussed. This will be followed by a discussion of the methodological strengths and limitations of the PhD project.

5.1. INCIDENCE RATES OF CHILDHOOD-ONSET PNES

Study I gives a population-based description of the incidence rates of pediatric-onset PNES.¹³¹ To the best of my knowledge, no prior study has reported the incidence rates of PNES in a nationwide cohort of children and adolescents with validated PNES. The overall IR of PNES among 5-17-year-old children and adolescents during the period 1996-2014 in Denmark was 2.4 per 100,000 person years. A progressive increase in incidence rates was observed between 2005-2014 with the IR peaking in 2014 at 7.4 per 100,000 person years. Females showed overall higher IRs than the males. During

the study period, females presented the highest IR in 2014 of 12.0 per 100,000 person years, while males showed a notably lower IR of 3.1 per 100,000 person years in the same year. When stratified by age at diagnosis, sixteen-year-old adolescents presented the highest IR for the total study period at 7.9 per 100,000 person years.¹³¹

As outlined in the literature review of this thesis, only five prior studies have investigated PNES incidence rates. Two studies reported incidence rates in children and adolescents, and three studies investigated adolescents and adults. The two studies reporting on children and adolescents (7-15-year-olds) were conducted in Australia and the UK in the study periods 2002-2003 and 2008-2009, respectively.^{46,47} These studies reported incidence rates based on national surveillance performed by consultant paediatricians, as well as child and adolescent psychiatrists in the UK study, who were asked to report the monthly number of cases assessed with a new diagnosis of conversion disorder. Case definition was based on DSM-IV criteria for conversion disorder, and all types of conversion disorders were included. Numbers of children and adolescents assessed to have a non-epileptic seizure disorder were reported; however, the diagnostic certainty of the diagnosis cannot be evaluated as the clinical information on which the diagnosis rests was not outlined. Thus, the numbers reported depend on the diagnostic skills of each consultant. The two studies reported IRs ranging from 0.4-0.5 per 100,000 person years.

The three studies reporting IRs in adolescents and adults were conducted in Iceland, the US and Scotland.⁵⁹ The Icelandic study was performed between 1992 and 1996, and all patients over 15 years of age in the country having new-onset seizures were examined with a video EEG.⁴⁸ The study found an IR of 1.4 per 100,000 person years for individuals aged 15-54 years. Individuals aged 15-24 years had the highest IR (3.4 per 100,000 person years), and females had the highest IR in this age group (5.9 per 100,000 person years). The US study from Hamilton county, Ohio, was performed as a retrospective study between 1995-1998 and included all individuals ≥ 18 years of age who were referred to an epilepsy specialist centre to have a video EEG examination.⁴⁹ The study reported an IR of 3.0 per 100,000 person years, which is higher than the numbers reported in the Icelandic study. The final study, conducted between 2006 and 2008, was from Scotland and covered a population of 367,566 individuals. Identifying all patients ≥ 13 years of age who had a video EEG-confirmed diagnosis of PNES at an epilepsy specialist clinic, the study reported an incidence at 4.9 per 100,000 person years.⁵⁰

Comparing the findings from Study I to the IRs reported in the previously published studies, the overall IR for the total study period (2.4 per 100,000 person years) was within the range of the previously reported IRs (0.4-4.9 per 100,000 person years). However, in Study I, the IRs rose to 7.4 per 100,000 person years in 2014, thus at a considerably higher level than previously reported.

When comparing the reported results, methodological differences in the studies should be noted as these may explain the varying IRs reported. Both the duration and the period varied across the studies, as did the inclusion criteria. The UK and Australian studies were performed on children and adolescents using surveillance

methodology and may therefore underestimate IRs.^{46,47} Variable response rates among the clinicians may lead to underestimation of IRs, and individual diagnostic practices may vary leading to further selection bias. The three studies including adult populations may also underestimate IRs because they relied on diagnostic criteria requiring video EEG examination.⁴⁸⁻⁵⁰ Hence, a selection bias may be introduced as individuals may have been diagnosed with PNES at a less specialized clinic without access to video EEG. This could mean that less complex cases with a clear PNES semiology were not included in these studies, and that the IRs may represent a population of highly selected cases from tertiary treatment units.

The IRs reported in Study I of this thesis may present a more true reflection of the IRs of paediatric-onset PNES in the general population. Children and adolescents in the PNES cohort were included based on an adapted version of the ILAE criteria for PNES,^{35,131} and included cases with an ictal video EEG testing as part of the diagnostic management as well as cases with a PNES diagnosis primarily based on the assessment performed by clinicians. Thus, the PNES cohort established in the present PhD project was recruited from both secondary and tertiary hospital settings, which reduced the risk of selection bias compared with prior studies.

The causal relationship underlying the rising IRs reported in Study I cannot be explored based on the data available to this project. The rising IRs may represent a true increase in the occurrence of PNES; however, other explanations may also explain the increase. Hence, more knowledge of PNES among the healthcare professionals may improve awareness and recognition of the disorder, and hence contribute to increasing IRs over time. Growing consensus on the diagnostic management and which ICD-10 diagnosis to register when establishing the diagnosis of PNES may further contribute to increasing IRs as the eligible study participants in Study I were identified based on register diagnoses. An increased level of precipitating factors such as experienced stress should also be considered as a heightened stress level may increase the risk of PNES among children and adolescents,¹⁴¹ as reflected in rising IRs. In total, several factors may help explain why rising IRs are observed among children and adolescents with PNES, and future studies should further explore the incidence rates of PNES.

5.2. CLINICAL CHARACTERISTICS

Study I outlines a clinical profile of characteristics observed in the cohort of children and adolescents with PNES and gives a presentation of differences between PNES with and without comorbid epilepsy.¹³¹ A number of findings described in prior smaller studies were replicated in this larger study sample, and new findings were reported regarding differences between PNES with and without epilepsy. The findings are discussed in the paper published based on study I.¹³¹ This section will first summarise results that are similar to those of previously published studies. This

will be followed by a discussion of previously published literature comparing PNES with and without comorbid epilepsy.

Study I confirmed previous literature reporting a preponderance of females among children and adolescents diagnosed with PNES.^{57,76} The frequent presence of accompanying psychiatric and specific socioenvironmental issues was confirmed as well. Study I also confirmed previous reports of school difficulties, learning difficulties and a need for school support in subjects diagnosed with PNES.⁷⁶ Around half of children and adolescents with PNES reported having experienced prior negative life events the most common of which were school bullying and interpersonal conflicts, whereas sexual and physical abuse were less commonly reported as also described in prior studies of pediatric-onset PNES.^{36,73} The range of seizure semiologies and the seizure characteristics observed in the PNES cohort were largely similar to those previously reported, and the only differences found were a higher occurrence of asynchronous movement semiology and a lower frequency of seizures (i.e. weekly) in Study I than in previous studies.^{32,39,51,61,142}

A total of 14.2% had comorbid epileptic seizures in the PNES cohort in Study I, while prior studies have reported numbers varying from 12% to 44%.^{42,69,143} The higher numbers reported in prior studies could be due to the fact that these studies analysed more complex cases having study participants recruited from specialized epilepsy clinics, whereas the results from Study I are more likely to reflect the true occurrence across a wider spectrum of PNES severity as our cases were recruited from all levels of hospital-based care. The findings from Study I demonstrate that the clinical characteristics associated with PNES with and without comorbid epilepsy were largely comparable. However, some differences were also observed. Hence, children and adolescents with PNES and coexisting epileptic seizures experienced a longer delay from onset of PNES to PNES diagnosis as well as a higher occurrence of intellectual disabilities and support in school. Thus, comorbid epileptic seizures appeared to challenge the process of establishing a diagnosis of PNES as well as warrant an assessment of possible learning disabilities.

The literature review performed as part of this thesis identified a small number of prior studies comparing pediatric-onset PNES with and without comorbid epilepsy, and all of the studies included small sample sizes. A UK study performed from 1987 to 1997 included 35 patients with PNES and 11 patients with PNES and comorbid epilepsy in the age range 6-18 years.⁷⁰ The study concluded that the prognosis of seizure remission was best in patients without comorbid epileptic seizures. A Danish study from 1997 examined nine patients with PNES and three patients with PNES and comorbid epilepsy in the age range 8-17 years.¹⁴⁴ The study demonstrated that mental retardation was present in all cases with coexisting epileptic seizures, which is in line with the results from Study I. A Brazilian study published in 2016 (i.e. information on the study period is not presented in the manuscript) included 32 patients with PNES and 21 patients with PNES and comorbid epilepsy in the age range 7-17 years.⁹⁷ The study reported that there was no difference in delay of time to diagnosis between the

two groups, whereas Study I reported an increased delay in time to diagnosis in patients with PNES and comorbid epilepsy. The presence of comorbid epileptic seizures could increase the complexity of the clinical assessment, which may be reflected in a longer delay in time to diagnosis. On the other hand, the presence of comorbid epileptic seizures could also be associated with earlier diagnosis of PNES as patients would be expected to be in closer contact with the healthcare system.⁹⁷ Finally, a study conducted in Italy from 2018 to 2019 included 15 patients with PNES, seven patients with PNES and comorbid epilepsy and 12 patients with epilepsy and no coexisting PNES.¹⁴⁵ All three groups were compared regarding psychopathological features. The study reported that patients with PNES (both with or without comorbid epilepsy) had higher rates of impairment reflected in the Children's Global Assessment Scale (C-GAS), had a higher occurrence of mood disorders, reported more negative life events, and had a lower resilience than patients only having epileptic seizures. Similar presentations of alexithymia and emotional dysregulation were observed in all three groups.

In total, prior evidence on the differences between PNES with and without comorbid epilepsy in children and adolescents is very limited. Regarding the adult population, a lack of evidence was also reported in a recent review of PNES with and without comorbid epilepsy.¹⁴⁶ The review identified a total of nine studies published from 2000 to 2015 and concluded that existing data were insufficient to reliably define variables associated with PNES and comorbid epilepsy.¹⁴⁶ Thus, further research is needed to clarify potential factors associated with PNES with and without comorbid epilepsy. This knowledge may qualify the challenging diagnostic process of distinguishing between PNES and epilepsy and may inform the discussion whether having epileptic seizures may be a predisposing factor for PNES.

5.3. PSYCHIATRIC COMORBIDITY

Study II was conducted as a nationwide matched cohort study. It showed that children and adolescents with PNES were at higher risk of being diagnosed with psychiatric disorders both prior to as well as in the 2-year period after their PNES diagnosis than children and adolescents with epilepsy as well as healthy controls.¹³⁷ The percentage of children and adolescents registered with a psychiatric diagnosis before receiving their PNES diagnosis was 39.8%, and 39.1% were diagnosed with an incident psychiatric diagnosis in the 2-year period after having received the PNES diagnosis. The findings from Study II demonstrated that pediatric-onset PNES was associated with a wide spectrum of psychiatric disorders the most common being adjustment disorders, SSRDs, emotional disorders and neurodevelopmental disorders.¹³⁷

When comparing the results from Study I and Study II, a difference is observed regarding the occurrence of psychiatric disorders prior to the PNES diagnosis. In Study I, 20.2% had a history of psychiatric disorders at the time of PNES diagnosis as opposed to 39.8% having a prior registered psychiatric diagnosis in Study II. A

plausible explanation for this difference could be that the data in Study I were extracted from medical records that relied on information documented by the clinicians who assessed the children and adolescents, and there may be limitations regarding the completeness of the data. The majority (89.6%) of the PNES cohort received their PNES diagnosis at a somatic department and clinicians may have failed to document the prior psychiatric history for several reasons. For example, paediatricians or neurologists may have been more prone to focus on prior somatic than psychiatric history when assessing the patients. Thus, the data abstracted from the medical records in study I is incomplete, and the numbers reported in study II must be considered more reliable as we expect data completeness to be higher in Study II than in Study I.

Prior studies have reported an occurrence of comorbid psychiatric disorders in children and adolescents with PNES varying from 16% to 100%.⁷⁶ This variation may be due to methodological differences in PNES inclusion criteria, differences in study populations and study settings in terms of level of hospital care and differences in how psychiatric disorders were assessed. Most prior studies on psychiatric comorbidity in pediatric-onset PNES were performed using small sample sizes and without comparison groups. Still, the literature review of this thesis identified four more comprehensive studies. Pooling the results of these studies allows us to give a thorough account of psychiatric disorders in children and adolescents with PNES. The four studies are discussed in the below paragraph, and methods and results are outlined, and parallels are drawn to the results of Study II.

A study from the US published by Plioplys et al.⁶⁴ in 2014 included 55 children and adolescents with PNES and their 35 siblings as well. The subjects were in the age range 8-18 years, and the study was conducted as a multisite study recruiting participants from tertiary epilepsy clinics. All PNES diagnoses were confirmed with a video EEG evaluated by a paediatrician with expertise in seizures, and a child psychiatrist assessed the PNES diagnosis. Comorbid psychiatric disorders were assessed using a semi-structured diagnostic instrument (K-SADS), and a blinded co-investigator assessed the comorbid diagnoses and viewed a recording of the semi-structured interview. The included children and adolescents with PNES had a mean age of 14.8 years and 71% were females; thus, the demographics were very similar to those of the PNES cohort in Study II. In the study by Plioplys et al.,⁶⁴ 29.1% had comorbid epilepsy; which is higher than reported for Study II (14.2%); this difference may impair the comparability of the study samples. All PNES cases in the study were assessed to have multiple psychiatric diagnoses, which was also the case for 45.7% of the siblings. Regarding specific diagnoses, significantly more of the PNES cases than of their siblings had anxiety, depression and PTSD. Among the PNES cases, 83% had anxiety, 43% had depression and 25% had PTSD. No significant differences between the groups were seen for ADHD and learning disorders; still, among PNES cases, 29% suffered from ADHD and 60% from learning disorders. Thus, compared to the results

from Study II, Plioplys et al. reported substantially higher numbers of psychiatric comorbidity in pediatric-onset PNES both overall and for specific diagnoses.

An Australian study performed by Kozłowska et al.⁸⁰ recruited 60 children and adolescents with PNES in the age range 8-17 years during the period 2011 to 2016. Patients were referred to a Psychological Medicine team for treatment after a neurology department had established the PNES diagnosis. The mean age at inclusion was 13.5 years, and 70% were females; thus, the population was younger than the population included in Study I. Psychiatric comorbidity in PNES cases was described based on DSM-IV criteria, but the paper supplied no information on whether clinicians used diagnostic instruments as part of their assessment. A total occurrence of any psychiatric disorder was not provided, but 37% had anxiety disorder, 12% had PTSD, 12% had panic disorder, 17% had depression, 5% had behavioural disorder and 2% had eating disorder. The numbers reported by Kozłowska et al.⁸⁰ are lower than the results reported by Plioplys et al.⁶⁴ but more similar to the results from Study II. Mood disorders were frequent; however, Kozłowska et al. did not clearly state whether the total range of psychiatric disorders had been assessed.

A third study from the US by Luthy et al.⁷⁸ was conducted as a retrospective cohort study using data from an administrative database of 49 North American Children's hospitals in the period 2004 to 2014. The study included children and adolescents in the age range 8-20 years who had a registered diagnosis of PNES or epilepsy. PNES cases were included based on a registration with either of the ICD-9 diagnoses "Conversion disorder" (ICD-9: 300.11) or "Other convulsions" (ICD-9: 780.39). PNES cases were excluded if, prior to their PNES diagnosis, they were registered in the database with chronic somatic disorder diagnoses, suicide attempts, infections, trauma or pregnancy. Furthermore, PNES cases were excluded if they had a concurrent, registered epilepsy diagnosis or somatization disorder. The same exclusion criteria applied to patients included in the epilepsy cohort of the study who were identified if they were registered with a diagnosis of epilepsy (ICD-9: 345.00-345.91). Thus, the study by Luthy et al.⁷⁸ defined their PNES and epilepsy cohort using a comprehensive retrospective register data approach, but several limitations challenge the generalizability of the results. The study focused on PNES cases without comorbid epilepsy as cases with concurrent epilepsy were excluded. A further selection bias was introduced since the exclusion criteria barred recruitment of patients with a broad range of prior somatic disorders and patients with a concurrent somatization disorder, which is reported to be a common pathology in children and adolescents with PNES.⁵⁷ Furthermore, Luthy et al.⁷⁸ did not validate the PNES diagnosis nor did they use matching when including the epilepsy cohort. Thus, the following results of this study should be interpreted with caution. A total of 399 patients were included in the PNES cohort, 72% were female and most were 14-16 years old. In the PNES cohort, the study demonstrated that 26% had anxiety disorder, 10% had bipolar disorder, 8% had depressive disorder and 8% suffered from a trauma or stress-related disorder. A total of 41% were reported to be registered with any of these disorders, and the remaining spectrum of psychiatric disorders were not investigated. Thus, mood disorders were common; still, several limitations of the

methodology of the study hamper comparison of the findings with the results demonstrated in Study II of this thesis.

Finally, a UK study performed by McWilliams et al.⁷⁷ studied 59 children and adolescents with PNES from 2012 to 2016. The study was a retrospective review of medical records from a tertiary children's hospital, and clinical assessment was performed by a multidisciplinary team from both psychiatry and neurology. The PNES diagnosis was assessed using video EEG and was based on a specialist's clinical evaluation. Diagnostic psychiatric assessment was performed involving a consultant psychiatrist and using ICD-10 diagnoses. A total of 63% were female and 37% had comorbid epilepsy diagnosis. A comorbid psychiatric disorder was identified in 50% of PNES cases, and 17% had comorbid autism spectrum disorder (ASD), 9% had an ADHD diagnosis and 7% had intellectual disability. PNES cases with ASD were significantly more likely to have ADHD and tics than PNES cases without ASD. McWilliams et al.⁷⁷ reported a lower percentage of females and a higher occurrence of comorbid epilepsy among cases with PNES than Study II. Though patients were recruited at a tertiary hospital, the reported occurrence of any psychiatric comorbid disorder was similar to the results of Study II which were based on cases from all levels of hospital-based care, but lower than reported by Plioplys et al.⁶⁴ Still, the reported occurrence of ASD was substantially higher than reported in Study II, which may be explained by the fact that neurodevelopmental disorders are more common among males than among females and are associated with epilepsy.^{120,147}

In summary, as suggested by previously published studies, the findings from Study II demonstrate an increased risk of psychiatric disorders in children and adolescents with PNES compared with children and adolescent with epilepsy as well as children and adolescents with no PNES or epilepsy. Study II outlines a broad spectrum of psychiatric disorders associated with PNES, as indicated in previously published literature. A thorough clinical psychiatric assessment of children and adolescents with PNES is important since unidentified psychopathology may perpetuate PNES and have a negative impact on both social and school functioning in the affected children and adolescents.

5.4. HOSPITAL SERVICE USE

Study III was performed as a nationwide matched cohort study and demonstrated that children and adolescents with PNES used more hospital services in the 2 years leading up to their PNES diagnosis and in the 2 years after having received their PNES diagnosis.¹⁴⁰ The majority of the contacts took place in somatic hospital settings, and somatic service use peaked in the year preceding the PNES diagnosis. After they had been diagnosed, children and adolescents with PNES continued to use more somatic services than the children and adolescents with epilepsy and HCs. Most of the children and adolescents with PNES had no registered contacts to psychiatric hospitals in the 2-year period after having received their PNES diagnosis.¹⁴⁰

Based on these findings, Study III thus shows that PNES in children and adolescents impose a considerable burden on the healthcare system, especially due to contacts in the somatic hospital setting. As mentioned in chapter one of this thesis, children and adolescents with epilepsy are known to have increased morbidity compared with children and adolescents from the general population.¹²¹ Study III now provides evidence that increased morbidity associated with childhood-onset PNES is also an important issue that warrants attention.

As mentioned above, most of the hospital services used by children and adolescents with PNES were offered by the somatic hospitals, and the majority of children and adolescents with PNES received no psychiatric hospital care after having received their PNES diagnosis. The design used in Study III did not allow us to elicit information on the cause leading to the hospital contact or the treatment. Thus, we were not able to conclude whether children and adolescents with PNES received relevant care or not; still, they continued to have a high use of hospital services after receiving their PNES diagnosis, which could indicate that relevant treatment was not supplied. In Denmark, children and adolescents with PNES have traditionally been managed solely in paediatric departments as treatment options in psychiatric care have been scarce. A survey of Danish neuro- and social-paediatricians demonstrated that only 13% found existing treatment options to be sufficient; nevertheless, only 23% of the neuro-paediatricians often referred their patients to child and adolescents psychiatric care.⁹⁹ The Danish Health Authority has recently outlined a clinical recommendation stating that the most severe cases of children and adolescents with functional disorders should be offered treatment in collaboration with the child and adolescent psychiatric departments.¹⁴⁸ Treatment options in Danish paediatric departments vary across the country with some paediatric departments offering psychological care as part of the treatment. However, the findings of Study II and Study III of this thesis suggest that a closer collaboration between somatic and psychiatric healthcare professionals is needed to ensure relevant treatment of both neurological and psychological symptoms. Ibeziako and colleagues has recently published a description of a clinical pathway for SSRDs in pediatric hospital settings,¹⁴⁹ which outlines a number of key steps from admission to discharge of children and adolescents with functional somatic symptoms in the attempt to provide a systematic standardized care. Clinical care pathways could give a standardization of care to ensure a close integrated multidisciplinary collaboration between the pediatric and child and adolescent psychiatric departments.

The literature review outlined in chapter one of this thesis identified a very limited number of prior studies on healthcare use in childhood-onset PNES. Still, the findings of these studies are in line with the findings of Study III, and they testify to an increased use of somatic emergency room visits and hospitalizations among patients with childhood-onset PNES compared with their siblings and with children and adolescents with epilepsy.^{63,64,96} The study by Luthy et al.⁷⁸, discussed in the section above on psychiatric comorbidity, reported total hospital costs to be higher for

children with epilepsy than for children with PNES; however, the study had several limitations introducing selection bias, and it only reported on costs associated with the incident hospital admission where the children received their PNES or epilepsy diagnosis.⁷⁸ The findings demonstrated in Study III included the complete use of hospital-based care covering a period from 2 years before until 2 years after the PNES diagnosis, thus providing results based on very robust and reliable data.

In total, the findings suggest that efforts are needed to reduce the healthcare use of children and adolescents with PNES and to ensure access to appropriate treatment, which may improve patient outcomes and lower hospital-based care costs. Specialized treatment approaches involving multidisciplinary, integrated physical and mental healthcare have been suggested in previous studies.^{18,86,103–106} Future research should focus on strengthening the evidence base of treatment of paediatric-onset PNES by developing treatment models and protocols that should be assessed in RCTs. Such research could improve treatment options and decrease the burden on healthcare systems associated with this disease.

5.5. STRENGTHS AND LIMITATIONS OF THE PHD PROJECT

It is important to acknowledge that all research methodology holds limitations, and these limitations may influence the findings and conclusions of the research undertaken. When conducting an observational cohort study, the internal and external validity should be assessed.¹⁵⁰ The internal validity describes how well a study can rule out alternative explanations of the demonstrated findings, also described as the degree of confidence in that potential confounders cannot explain the observed results. The external validity is the extent to which the demonstrated findings can be generalized beyond the study sample. This section will discuss the strengths and limitations of the methodology used in the three studies of this dissertation.

A great strength of this PhD project is its population-based design, the use of nationwide data and the comprehensive systematic validation of individuals included in the PNES cohort. The use of register data enabled inclusion of a large study sample over a period spanning 2 decades and allowed inclusion of two matched comparison groups. Every citizen in Denmark has access to public healthcare free of charge, and since all hospital-based service use is documented in the Danish nationwide patient registries,¹²⁸ the risk of selection bias is minimized and the external validity of the register data is considered to be high.

The methodology used when establishing the PNES cohort in Study I had many strengths. Study participants were identified using two register diagnoses and they were recruited from both specialized tertiary care and secondary less specialized hospital care. A total of 96% of the eligible hospital departments accepted to participate in the study. Medical records were retrieved for 426 (94%) of the eligible

study participants. Furthermore, a thorough validation of the PNES diagnoses was performed, including a co-rating performed by both a consultant child and adolescent psychiatrist and a consultant neurologist.

Still, a number of limitations should be noticed. Two register diagnoses (ICD-10: F44.5 and R56.8G) were chosen as a definition of PNES. As previously outlined, consensus regarding which ICD-10 diagnoses to use when diagnosing PNES is lacking,¹² and a number of different register diagnoses may have been used to define PNES throughout the study period. On this background, an uncertain number of paediatric PNES cases may have been missed when establishing the cohort, which could bias the reported incidence rates and lead to a possible underestimation. Furthermore, a possible selection bias could also exist, as cases registered under different diagnoses may have other clinical characteristics. Nevertheless, the validation of the two included register diagnoses showed a high PPV, and using less specific register diagnoses would have made the number of study participants too large to ensure a validation of each participant as part of this PhD project due to pragmatic considerations.

The case validation included the use of an adapted version of the ILAE criteria.³⁵ The adapted criteria included clinical characteristics and witnessed seizure semiology, whereas EEG testing was necessary only to achieve the highest level of diagnostic certainty for PNES. The criteria were adapted to enable inclusion of the PNES cohort from both secondary and tertiary hospital-based care settings, since access to video EEG testing mainly exists in tertiary care in Denmark. The aim was to include a less selected sample of PNES cases, as most prior studies have included small samples from tertiary care, possibly raising issues regarding the external validity as these cases could be expected to be more severe and have higher morbidity. The gold standard of a PNES diagnosis is to have an ictal video EEG confirming the diagnosis; however, only including patients having undergone ictal video EEG testing would have decreased the generalizability to paediatric-onset PNES in the general population.

We based validation of the PNES diagnosis and the description of the clinical characteristics in Study I on data abstracted from medical records by the primary investigator (the PhD candidate, ASH). The quality of these data is closely linked to the meticulousness with which they have been recorded by the healthcare professionals, which means that issues may exist regarding their completeness. Still, the rating of the PNES diagnosis included an assessment of whether the medical record data were sufficient to perform the rating, and only nine 9 cases were excluded based on these considerations.

A limitation of Study I was the lack of a comparison group. It could have been interesting to compare the clinical characteristics reported in the study to the characteristics of either a group of children and adolescents with epilepsy or a group of HCs, as this could have disclosed the strength of the association with PNES. The study design in Study II and Study III enabled the inclusion of comparison groups, and matching was used to avoid possible confounding introduced by differences in

gender and age distribution as well as year of inclusion in the included study populations and to increase the internal validity of the findings. It should be noted that children and adolescents with epilepsy as well as HCs represent highly selected study samples due to matching on gender and age, and it is important to be careful not to generalize the numbers reported in Study II and Study III to all cases of epilepsy and children and adolescents from the general population.

An additional strength is the long study period, lasting 2 decades, which was possible due to the retrospective register-based research design. The study period, 1996 to 2014, was chosen for two reasons. First, the ICD-10 diagnostic system was implemented in Denmark in 1995, and the shift from the ICD-8 to the ICD-10 diagnoses could introduce data inconsistency in the initial phase due to changes in coding practice. Thus, the study period was initialized in 1996 to allow a washout period and thereby diminish the risk of information bias. Second, the study period was set to end in 2014 to ensure completeness of the register data during the 2-year follow-up period requiring data capture up until 2016.

Every Danish citizen is registered in national healthcare registries. Nationwide data on hospital-based care are therefore available, and data may be extracted with a minimal risk of loss to follow-up since individuals are censored from the registries only in case of death or upon immigration from Denmark. This reduces the risk of bias arising from sampling as well as attrition.

As described above, the PPVs of the two PNES inclusion diagnoses used in Study I were high,¹³¹ and previous literature has reported that the PPV of the epilepsy register diagnosis is high as well.¹⁵¹ Thus, the external validity must be considered high in both the PNES cohort and the epilepsy control group. The validity of the included psychiatric ICD-10 diagnoses has been investigated for some of the diagnoses, showing varying PPVs,^{152,153} but the majority of the included psychiatric diagnoses have not been validated in a paediatric population. Still, children and adolescents who were registered with a psychiatric hospital contact and a psychiatric diagnosis must be considered to have passed a disease severity threshold warranting psychiatric hospital-based care. Some level of misclassification may be present in the included data on psychiatric diagnoses, but the numbers reported in Study II are expected to reflect a degree of psychopathology too severe to be treated in primary care, thus demonstrating the presence of severe mental health problems in the study populations.

For Study III, the external validity must be considered high, as register data cover all hospital-based service use in the PNES cohort and as censoring was minimal in both the epilepsy control group and HCs after study inclusion. Danish register data are considered to have a high completeness; however, inconsistencies due to errors in data documentation or changes in coding practice are inevitable.¹²⁸ These errors are considered random and equally present among individuals in the study, and data management conducted in Study III raised no concerns that could question this assumption.

Overall, the PhD project had many strengths, but limitations were also noted that should be considered when interpreting the findings. Still, all three studies on which the present PhD dissertation is based had high internal and external validity, wherefore the findings of the PhD project may be considered trustworthy and applicable to the real world.

CHAPTER 6. CONCLUSIONS

Psychogenic nonepileptic seizures (PNES) in children and adolescents lead to distress and impairment with school absenteeism and disruption of daily functioning for the affected patients. PNES impose a profound burden on patients and their families; even so, a treatment gap is described as diagnosis and treatment of the disorder intersect somatic and mental healthcare. Paediatric-onset PNES can be difficult to recognize and diagnose in the clinical setting as seizure symptoms mimic more commonly encountered disorders like epilepsy. This may delay diagnosis and lead to increased use of healthcare services due to misdiagnosis and repeated clinical examinations. Nevertheless, the literature review of this thesis demonstrated that previous knowledge on paediatric-onset PNES is based on a limited level of evidence which warrants further research.

This PhD project aimed to establish a large cohort of children and adolescents with PNES and thereby increase the evidence base regarding incidence, characteristics and morbidity of childhood-onset PNES. Based on a population-based cohort design, the findings demonstrate a marked increase in the number of children and adolescents diagnosed with PNES from 1996 to 2014 in Denmark. Incidence rates were observed to be highest in female adolescents, and the highest rates were reported in 2014. More than every tenth paediatric patient with PNES had a concurrent epilepsy diagnosis, and a larger fraction of children and adolescents with comorbid epilepsy had intellectual disabilities, received support in school and were diagnosed with PNES later than the children and adolescents without comorbid epilepsy. Thus, comorbid epileptic seizures appeared to increase morbidity.

Furthermore, based on the results from this PhD project, it can be concluded that children and adolescents with PNES are at higher risk of psychiatric disorders than children and adolescents with epilepsy and children and adolescents with no PNES or epilepsy. Elevated risks were observed for a wide spectrum of psychiatric disorders, which underline the importance of a careful psychiatric assessment and an individualized treatment plan when managing childhood-onset PNES.

Finally, the PhD project demonstrated that children and adolescents with PNES have a higher use of hospital services in the 2-year period before and 2-year period after receiving their PNES diagnosis, compared with children and adolescents with epilepsy and children and adolescents with no PNES or epilepsy. Hospital services were provided mainly by somatic hospitals, and the majority of children and adolescents received no psychiatric hospital care after their PNES diagnosis. The findings underscore that childhood-onset PNES impose a considerable burden to hospital-based care and indicate that children and adolescents with PNES do not receive relevant care after their PNES diagnosis, since the offered treatment was not able to diminish the higher use of hospital services.

In conclusion, the present PhD project is the first of its kind to establish a nationwide validated cohort of children and adolescents with PNES. The increasing incidence rates and the associated morbidity, in terms of psychiatric disorders and primarily somatic hospital service use demonstrated in paediatric-onset PNES, suggest a need for an integrated multidisciplinary care approach to ensure proper recognition and management of this young group of patients.

CHAPTER 7. CLINICAL IMPLICATIONS AND FUTURE RESEARCH

The present thesis reported rising incidence rates of paediatric-onset PNES, a high associated burden of psychiatric disorders and elevated hospital service use in children and adolescents with PNES. These findings highlight that pediatric-onset PNES should be recognized as a disorder in need of relevant treatment options; moreover, the heterogeneous manifestation and wide spectrum of psychiatric disorders associated with paediatric-onset PNES suggest a need for integrated physical and mental healthcare pathways. This need is also voiced in extant literature, and it is recommended that management and treatment of functional disorders, including PNES, take place in close collaboration between somatic and psychiatric healthcare professionals.

The high occurrence of psychiatric disorders in children and adolescents with PNES indicates that careful psychiatric evaluation should be considered in every young person affected by PNES to determine if psychiatric treatment is needed. If psychiatric care is not deemed to be necessary, the psychiatrist's role could be to give expert advice and supervision to the patient's supporting network including the healthcare professionals in charge of the patient's treatment. A stepped-care approach to management of PNES could help clarify the care pathways and bridge the gap between mental and physical healthcare, as well as ensure that patients receive relevant treatment. Additionally, the high risk of developing psychiatric disorders in the years following the PNES diagnosis could suggest a need for continued close collaboration with the mental health specialist to monitor any new psychopathology. Improved clinical care pathways and treatment guidelines for paediatric-onset PNES may be a way forward to reduce morbidity in this young patient group, which may as well decrease the burden of healthcare utilization.

The growing interest in paediatric-onset PNES is reflected in the emerging research evidence seen in recent years; still, further research is warranted as the current level of evidence remains limited. Future research should address variables associated with paediatric-onset PNES to improve recognition of this disorder and help distinguish PNES from other paroxysmal disorders like epilepsy. A prospective observational cohort study design could be used to outline risk factors and clinical characteristics in children and adolescents developing PNES compared with those developing epilepsy and with children and adolescents from the general population. Psychiatric morbidity in children and adolescents with PNES was described in detail in this thesis; however, potential somatic morbidity associated with pediatric-onset PNES should also be explored in further detail. Regarding the healthcare utilization in children and adolescents with PNES, prior lifetime healthcare use including contacts to general practitioners in primary care and long-term follow-up studies on healthcare utilization

could further clarify the associated burden of healthcare use and inform future provision of healthcare services to this group of patients.

Future research should also explore clinical care pathways and assess treatment protocols for paediatric-onset PNES. Randomized clinical trials on treatment exploring outcomes such as healthcare use, daily functioning, seizures remission and quality of life could improve the evidence base for treatment guidelines to be implemented in the clinical setting. A multi-centre study could offer the opportunity to include a larger number of children and adolescents with PNES across hospital-settings in Denmark or across countries, and this could enable more comprehensive trials of integrated care approaches to help coordinate the clinical pathways and bridge the gap between the somatic and psychiatric settings.

Finally, knowledge dissemination and growing awareness of PNES are important to make patients, their families, and lay people more familiar with this disorder. Healthcare professionals also lack knowledge about PNES; thus, training in management of functional disorders typically constitutes only a very small part of the healthcare professionals' curriculum. Patients with PNES and their families often experience stigma, which may be addressed through information facilitating a change in the attitude among lay people and healthcare professionals. Increased awareness can be achieved by developing patient information leaflets or webpages, by giving talks on PNES in local communities, by ensuring proper formal training of clinicians in assessment and management of PNES, and by developing national consensus guidelines on clinical care pathways and treatment of paediatric-onset PNES. An important step forward is to increase awareness of PNES and highlight the fact that PNES should be recognized as a complex disorder in need of access to multidisciplinary treatment options to decrease the burden of impairment, distress and morbidity placed on this young group of patients.

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APPENDICES

Appendix A. Literature search

Appendix B. REDCap Case Report Form

Appendix C. Data from medical records

Appendix D. Psychiatric disorder categories

Appendix A. Literature search

Definition of search terms by block building strategy:

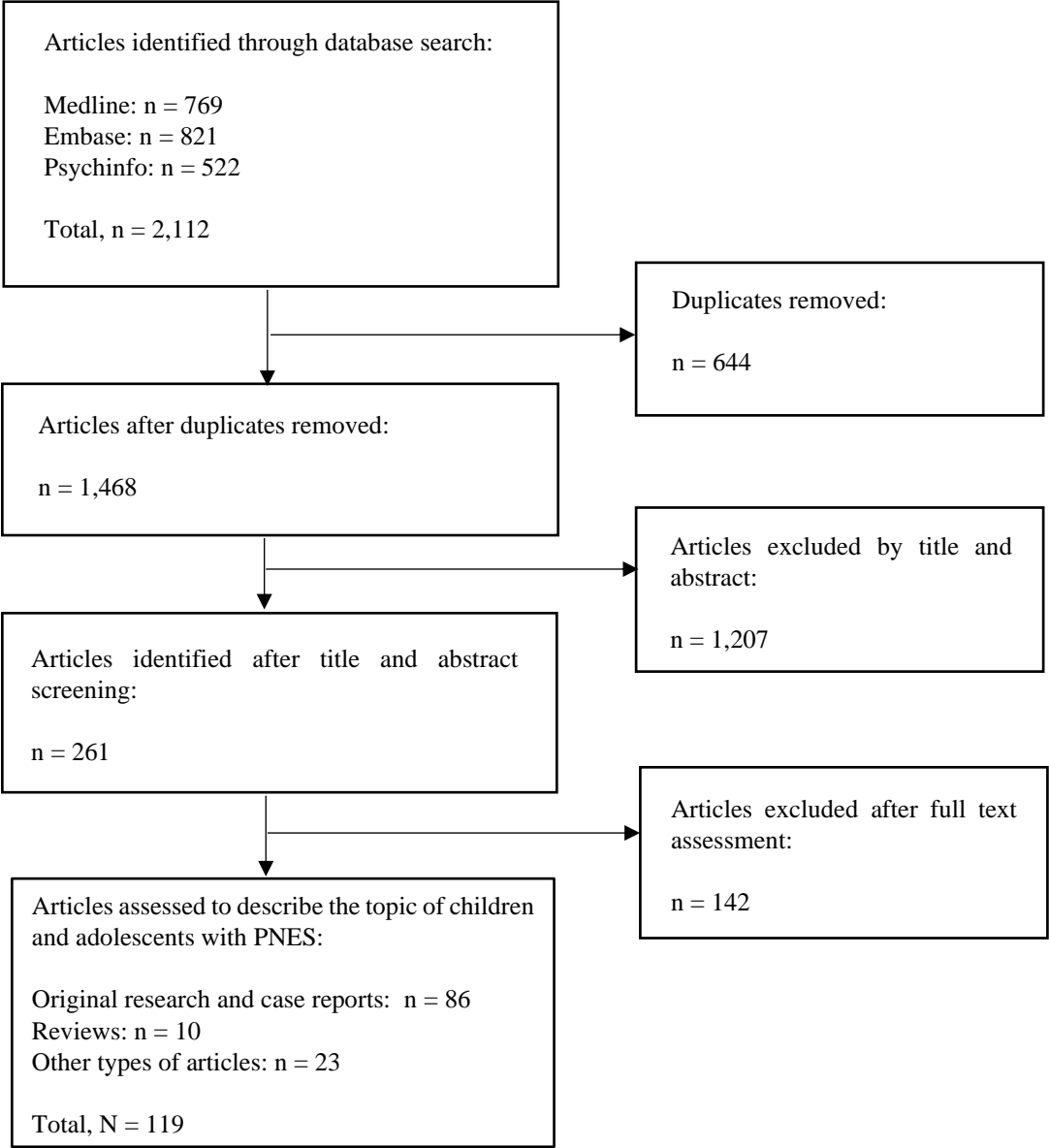
AND		
OR	Aspect 1: PNES	Aspect 2: Children and adolescents
	PNES Psychogenic nonepileptic seizures Psychogenic non-epileptic seizures Psychogenic non epileptic seizures Pseudoseizures Functional seizures Nonepileptic seizures Non-epileptic seizures Non epileptic seizures NEAD Nonepileptic attack disorder Non-epileptic attack disorder Non epileptic attack disorder	Paediatric Pediatric Children Adolescents

Results of the database search:

Databases	Search performed
Medline	Terms: text words and MeSH Restrictions: Years: none. Language: none. Date of last search: 1 October, 2020 Number of results: 769
Embase	Terms: free text and Emtree Restrictions: Years: none. Language: none. Publication type: no conference abstracts. Date of last search: 1 October, 2020 Number of results: 821
PsychINFO	Terms: key words and Thesaurus Restrictions: Years: none. Language: none. Date of last search: 1 October, 2020 Number of results: 522

Appendix A – continued.

Flowchart of the literature review:



Appendix B. REDCap Case Report Form

Confidential

Pediatric onset PNES
Page 1

PNES

REDCap id

Patient ID number (P-__)

Rating Scale and Case Report Form: An investigation of the diagnosis of PNES and a description of baseline characteristics in a Danish national cohort of children and adolescents

Date of rating (DD/MM/YY)

Investigator initials

- ☐ ASH
☐ CUR
☐ JC

ID/journal data

Gender

- ☐ Female
☐ Male

Hospital code (H-__)

Department code (D-__)

Region of Hospital

- ☐ North Denmark
☐ Central Jutland
☐ South Denmark
☐ Zealand
☐ Capital Area

Hospital department

- ☐ Pediatrics
☐ Neurology
☐ Child and Adolescent Psychiatry
☐ Other

Diagnosis

Inclusion register diagnosis

- ☐ F44.5
☐ R56.8G

Inclusion date (DD/MM/YY)

Start date of assessment period (DD/MM/YY)

End date of assessment period (DD/MM/YY)

Inclusion register diagnosis also found in the medical record

☐ Yes
☐ No

Diagnosis given as in- or outpatient

☐ Inpatient
☐ Outpatient

1. Patient History

1.1 Reason for referral to hospital (more than one cross possible)

☐ Seizures
☐ Fainting or dizziness
☐ Other reason
☐ Not described

If listed "other" reason for referral to hospital please describe which:

1.2 History of illness prior to PNES diagnosis

	Yes	No	Not described
Epileptic disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Head trauma	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other functional disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other severe somatic illness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychiatric disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

1.3 Family history of illness (only if 1. Generation: dad/mom/siblings)

	Yes	No	Not described
Epileptic disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
PNES	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other functional disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other severe somatic illness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychiatric disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

1.4 Early neurological complications

	Yes	No	Not described
Born < 37 gestational weeks	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Birthweight < 2500 g	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Low Apgar score (Apgar score < 7 at 5 and 10 minutes)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Permanent neurological sequelae due to birth complications described	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Delayed psychomotor development described	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

1.5 Current level of functioning: school/work

	Yes	No	Not described
Currently a school student	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If school student: attending primary school	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If school student: attending secondary school	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If school student: at expected class level corresponding to age	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If school student: problems described with school truancy, school refusal or sick leave	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If not school student: currently employed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If employed: problems described with high rates of sick leave	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If not school student: attending kindergarten or daycare	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

1.6 Current level of functioning: general markers

	Yes	No	Not described
Low IQ (< 70)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Learning difficulties	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Indicators of social isolation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Criminal behaviour	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Substance abuse	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

1.7 Living situation (more than one cross possible)

- ☐ Living with parents
☐ Living at residential school
☐ Living alone
☐ Living in fostercare
☐ Living at childrens institution
☐ Other living situation
☐ Not described

If listed "other" living situation please describe

1.8 Other family characteristics

	Yes	No	Not described
Adoption child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Parents divorced	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mother receiving social transfers	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Father receiving social transfers	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

1.9 Other somatic symptoms described out of context with the seizures

	Yes	No	Not described
Symptoms from heart and lung (CP symptoms)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Symptoms from abdomen and intestines (GI symptoms)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Symptoms from muscles and joints (MS symptoms)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
General symptoms	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Personal Trauma and Suicidal Behaviour

1.10 Personal trauma or stressful events described

- ☐ Yes
☐ No
☐ Not described

If personal trauma or stressful events described: please list which (more than one cross possible)

- ☐ Described with a stressful daily life (i.e. exams, school, socially active, hobbies)
☐ Victim of school bullying
☐ Victim of sexual abuse
☐ Victim of physical abuse
☐ Victim of psychological abuse
☐ Stressful interpersonal conflict
☐ Stressful divorce of parents
☐ Parent sent to prison
☐ Parent with substance abuse
☐ Exposed to experiences of child neglect
☐ Close relative with severe physical or psychiatric disorder
☐ Death of family member or close friend
☐ Involved in accident
☐ Witness to violence
☐ Other

If listed "other" personal trauma or stressful events please describe

1.11 Suicidal behaviour

- ☐ Yes
☐ No
☐ Not described

If suicidal behaviour: please list which (more than one cross possible)

- ☐ Previous or current suicidal attempt
☐ Previous or current suicidal ideations
☐ Previous or current self-harm without suicidal intention
☐ Previous or current self-harm of unknown intention

1. Clinical information

1.13 CT/MRI performed

- ☐ Yes
☐ No
☐ Not described

1.14 CT/MRI result if performed (list most recent result, and please list MRI result if performed - otherwise CT result)

- ☐ Normal
☐ Changes clinically relevant for epilepsy
☐ Unspecific changes
☐ Not described

1.15 Other examinations:

	Yes	No	Not described
Relevant blood tests performed (blood glucose, blood count, electrolyte test, kidney/liver/thyroid function, infection tests)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Normal blood test result if performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Electrocardiography performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Normal electrocardiogram if performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
General somatic examination performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
General somatic examination normal if performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Neurological assessment performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Neurological assessment by neurologist or pediatrician	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Neurological assessment normal if performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychiatric assessment performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychiatric assessment by psychiatrist	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychiatric assessment normal if performed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

1.16 Prior treatment initiated

	Yes	No	Not described
Support established in home setting: social services	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Support established in school or daycare: special education or support, PPR	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychotherapy treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Physiotherapy treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Prior medication with antiepileptic drugs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Current medication with antiepileptic drugs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Prior medication with psychopharmacological drugs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Current medication with psychopharmacological drugs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Seizure characteristics and semiology

2.11 Time from first seizure to current PNES diagnosis	<input type="radio"/> 0-½ year <input type="radio"/> ½-1 year <input type="radio"/> 1-2 years <input type="radio"/> 2-3 years <input type="radio"/> 3-4 years <input type="radio"/> 4-5 years <input type="radio"/> >5 years <input type="radio"/> Not described
2.12 Current frequency of PNES seizures	<input type="radio"/> daily <input type="radio"/> weekly <input type="radio"/> monthly <input type="radio"/> yearly <input type="radio"/> Not described
2.13 Typical duration of PNES seizures	<input type="radio"/> 0-5 minutes <input type="radio"/> 5-30 minutes <input type="radio"/> 30-60 minutes <input type="radio"/> > 60 minutes <input type="radio"/> Not described
2.14 Pre-ictal hyperventilation	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not described
2.15 Ictal hyperventilation	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not described
2.16 PNES seizures typically in context with stressful situations	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not described

If listed "yes" to PNES seizures typically in context with stressful situations, please describe which situations

Specific trigger described in context with the first experienced seizure

- ☐ Yes
☐ No
☐ Not described

If listed "yes" to specific trigger, please describe which

2.2 Seizure witnessed by (more than one cross possible)

- ☐ A. Experienced clinician (i.e. neuropaediatrician or neurologist)
☐ B. Non-specialized clinician observation
☐ C. Patient or witness report
☐ Not described

2.3 Seizure semiology typical of PNES

	Yes	No	Not described
Silent seizures: long-term contactless period	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long duration of seizure: more than five minutes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Not during sleep	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Occurrence in the presence of others	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Asynchronous movements	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Emotional features during seizure: smiling, laughing, crying, gasping	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urinary/fecal incontinence and tongue biting not present	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
No physical injury due to falling	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fluctuating seizure pattern (not stereotype seizure)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Attained consciousness/response when addressed during seizure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Gradual onset	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Head movement from side-to-side	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Vocalization/ictal crying, especially in the middle or ending of the seizure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Closed eyes/resist eyelid opening	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hip movements/pelvic thrusting	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Rapid postictal reorientation

☐☐☐**3. Electroencephalography (EEG)**

3.1 EEG performed prior or in context with the diagnostic assessment

- ☐ Yes
☐ No
☐ Not described

3.2 EEG subtype if performed (more than one cross possible)

- ☐ Ictal-EEG
☐ Interictal-EEG
☐ Ictal-video-EEG
☐ Interictal-video-EEG

3.3 EEG result if performed: (more than one cross possible)

	Ictal	Interictal
Normal activity	<input type="checkbox"/>	<input type="checkbox"/>
Abnormal epileptiform activity (both generalized and focal)	<input type="checkbox"/>	<input type="checkbox"/>
Abnormal non-epileptiform activity	<input type="checkbox"/>	<input type="checkbox"/>
EEG description not found	<input type="checkbox"/>	<input type="checkbox"/>

3.4 V-EEG result if performed (more than one cross possible)

	Ictal	Interictal
Normal activity	<input type="checkbox"/>	<input type="checkbox"/>
Abnormal epileptiform activity (both generalized and focal)	<input type="checkbox"/>	<input type="checkbox"/>
Abnormal non-epileptiform activity	<input type="checkbox"/>	<input type="checkbox"/>
EEG description not found	<input type="checkbox"/>	<input type="checkbox"/>

4. Rating: Abridged criteria for diagnostic level of certainty for PNES (based on the ILAE criteria)

4.1 Rating: Patient history and clinical information found consistent with PNES

- ☐ Yes
☐ Not PNES
☐ Insufficient information to perform rating

4.2 Rating: PNES-consistent characteristics and semiology

- ☐ A. Evaluated by experienced clinician in diagnosis of seizure disorders as witness or from video-recording
☐ B. Evaluated by non-specialized clinician as witness or from video-recording
☐ C. Described by patient or witness report
☐ Not PNES
☐ Insufficient information to perform rating

4.3 Rating: EEG result

- ☐ A. Ictal Video-EEG: with no epileptiform activity on EEG and with typical PNES semiology
☐ B. Ictal EEG if performed: no epileptiform activity on EEG during a typical seizure
☐ C. Interictal EEG/Video-EEG if performed: no epileptiform activity
☐ Performed showing epileptiform activity
☐ Not performed
☐ Insufficient information to perform rating
-

Appendix 1: Case definition - Abridged criteria based on ILAE

[Attachment: "Abridged criteria for diagnostic level of certainty for PNES.pdf"]

4.4 Rated diagnostic level of certainty (see Appendix 1)

- ☐ Documented
☐ Clinically established
☐ Probable
☐ Possible - likely yes
☐ Possible - likely no
☐ Not PNES
☐ Insufficient information
-

4.5 Case PNES conclusion (see Appendix 1)

- ☐ Confirmed case
☐ Not confirmed case
-

4.6 Rated to have co-existing PNES and epilepsy

- ☐ Yes
☐ No
☐ Maybe
-

4.7 If rated "Possible - likely no" or "Not PNES" please write a proposed other diagnoses or a comment on why the criteria are not fulfilled

4.8 If rated "Insufficient information" please write a comment on what is missing in order to perform the rating

5.0 ICD-10 criteria for the diagnosis F44.5 Dissociative seizures:

	Yes	Likely yes	Likely no	No
G1. No evidence of a physical disorder that can explain the symptoms that characterize the disorder (but physical disorders may be present that give rise to other symptoms)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
G2. Convincing associations in time between the symptoms of the disorder and stressful events, problems or needs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
A. The general criteria (G) for dissociative disorder (F44) must be met	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
B. Sudden and unexpected spasmodic movements, closely resembling any of the varieties of epileptic seizures, but not followed by loss of consciousness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
C. Criterion B is not accompanied by tongue-biting, serious bruising or laceration due to falling, or incontinence of urine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Criteria for F44.5 fulfilled (G1+G2+A+B+C)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

6.0 DSM-5 criteria for Conversion Disorder 300.11 (Functional Neurological Symptom Disorder)

	Yes	Likely yes	Likely no	No
A. One or more symptoms of altered voluntary motor or sensory function	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
C. The symptom or deficit is not better explained by another medical or mental disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important functioning or warrants medical evaluation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Specification: With attacks or seizures	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Specification: Acute episode (Symptoms present for less than 6 months)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Specification: Persistent (Symptoms occurring for 6 months or more)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Specification: With psychological stressor (specify stressor)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Criteria for 300.11 fulfilled (A+B+C+D)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Appendix C. Data from medical records

Data extracted	Definition
Clinical examinations	<p>EEG: subtype performed (ictal-EEG, interictal-EEG, ictal-video-EEG, interictal-video-EEG) and result (normal activity, abnormal epileptiform activity (both generalized and focal), abnormal non-epileptiform activity, EEG description not found).</p> <p>Cerebral MRI/CT: result (normal, changes clinically relevant for epilepsy, unspecific changes, not described).</p> <p>Neurological assessment: result registered if performed (normal: yes/no), and whether performed by neurologist or pediatrician.</p> <p>Psychiatric assessment: result registered if performed (normal: yes/no), and whether performed by a psychiatrist.</p>
Hospital information	<p>Type of hospital department: pediatric, neurology, child and adolescent psychiatric or other type of department.</p> <p>In- or outpatient status: admitted as inpatient or outpatient.</p> <p>Reason for referral: seizures, fainting or dizziness, other reason or not described.</p>
Seizure characteristics	<p>Time from onset to diagnosis was defined as the time from the first seizure reported in the patient history and up to the diagnosis of PNES.</p> <p>Frequency and duration of seizures were registered based on the information described in closest proximity to the time of inclusion.</p> <p>Stress in context with seizures included any description of being stressed in close proximity with having seizures.</p> <p>Trigger in context with onset of seizures included any event defined by the clinicians in the medical notes as a possible trigger.</p>
Seizure semiology	<p>In presence of others: seizure while other people around.</p> <p>Not during sleep: no seizures while sleeping.</p> <p>Asynchronous movements: asynchronous movements of limbs.</p> <p>Long duration: seizures lasting more than five minutes.</p> <p>Silent seizures: dialeptic seizures characterized by impaired consciousness and no motor activity.</p> <p>Rapid postictal orientation: regained consciousness within few minutes after the seizure.</p> <p>Gradual onset: seizure beginning with mild symptoms and becoming more severe gradually.</p> <p>No incontinence/tongue biting: no urinary or fecal incontinence and tongue biting present during seizure.</p> <p>Fluctuating pattern: seizure symptoms varying in type and severity during the seizure.</p> <p>Closed eyes: resist eyelid opening.</p> <p>Attained consciousness: response when addressed during seizure.</p> <p>No physical injury: due to falling or self-harm during seizure.</p>

Appendix C – continued.

Data extracted	Definition
Seizure semiology	<p>Ictal hyperventilation: abnormal increased respiratory rate during seizure.</p> <p>Pre-ictal hyperventilation: abnormal increased respiratory rate just before onset of the seizure.</p> <p>Emotional features: smiling, laughing, crying or gasping during seizure.</p> <p>Head movement from side-to-side.</p> <p>Hip movements: pelvic thrusting.</p> <p>Vocalization/ictal crying: especially in the middle or ending of the seizure.</p>
History of illness	<p>Patient history of illness: prior epilepsy diagnosis (defined as any type of epileptic disorder), prior psychiatric diagnosis (defined as any psychiatric disorder), and self-harm behavior prior to the diagnosis of PNES (defined as any suicidal attempt, suicidal ideations or self-harm).</p> <p>Family history of illness: prior epilepsy or psychiatric diagnosis as defined for patient history of illness. Registered for any first-generation family member: father, mother or sibling.</p>
Prior treatment	<p>Included: psychotherapy (defined as any contact to a psychotherapist), and prior use of psychopharmacological or anti-epileptic medicine.</p>
Level of functioning	<p>School problems: defined as any school truancy, school refusal or sick leave.</p> <p>Support in school: defined as any special education or contact to a school psychologist.</p> <p>Low IQ: defined as a described intelligence quotient below 70.</p> <p>Specific learning difficulties: defined as any problems with basic skills (reading, writing or math as well as organization or time planning).</p>
Family characteristics	<p>Included: The living situation (living with parents or living in foster care/children's institution), whether the parents were divorced, and if support was provided in the home by the social services.</p>
Negative life events	<p>The presence of negative life events prior to the diagnosis of PNES was identified based on a defined list of selected sub-items from the Childhood Traumatic Events Scale (Childhood Trauma Questionnaire, CTQ), and the Adverse Childhood Experiences International Questionnaire (ACE-IQ).</p>

(Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; CT, computed tomography; IQ, intelligence quotient.)

Appendix D. Psychiatric disorder categories

Definition of psychiatric disorder categories.

Psychiatric disorders	ICD-10 codes	ICD-8 codes
Emotional disorders (includes anxiety, OCD and depression, bipolar disorder)	F30-F39 F40-F42 F93, F98 (excluding DF98.8C)	296.x9 (excluding: 296.89), 298.09, 298.19, 300.49, 301.19 300.x9 (excluding: 300.49, 300.5-7)
Adjustment, PTSD and attachment disorders	F43, F94	307, 308.4
Neurodevelopmental disorders (ASD, ADHD, Tics/Tourettes, ODD/CD)	F84, F88-F89 F90-F92, F95 DF98.8C	299.00, 299.01, 299.02, 299.03 306.1, 306.x9, 308.xx (excluding: 306.1, 306.3, 308.4)
Intellectual and specific learning disabilities	F70-F79, F80-83	311.xx, 312.xx, 313.xx, 314.xx, 315.xx, 306.1
Somatic symptom and related disorders (excluding PNES)	F44.XX (excluding F44.5), F45, F48	300.5-7 305.xx (excluding 305.8, 305.9)
Personality disorders	F60, F61	301.x9 (excluding: 301.19), 301.80, 301.81, 301.82, 301.84
Psychotic disorders (includes schizophrenia, schizotypal, schizoaffective, and other psychotic disorders)	F20-F29	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83
Eating disorders (includes anorexia nervosa and bulimia nervosa)	F50	306.50, 306.58, 306.59
Self-harm	X60-X84	E950-E959, E980-E989
Substance use	F10-F19	291, 294.3x, 303.x9, 303.20, 303.28, 303.90, 304.x9

Definition of emotional and neurodevelopmental disorder subgroups.

Psychiatric disorder	Subgroups	ICD-10	ICD-8
Emotional disorders	A. Anxiety disorders, incl. phobic, generalized and panic anxiety B. Mood disorders C. OCD	A. F40, F 41, F93.1, F93.2, F93.8 B. F30-F39 C. F42	A. 300.0-2, 300.4 B. 296.x9 (excluding: 296.89), 298.09, 298.19, 300.49, 301.19 C. 300.3
Neurodevelopmental disorders	A. ADHD, ADD B. ASD C. Conduct disorders D. Tic disorders	A. F90, F98.8C B. F84 C. F91 D. F95	A. 308.3 B. 299.00, 299.01, 299.02, 299.03 C. 308.1-2 D. 306.2

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